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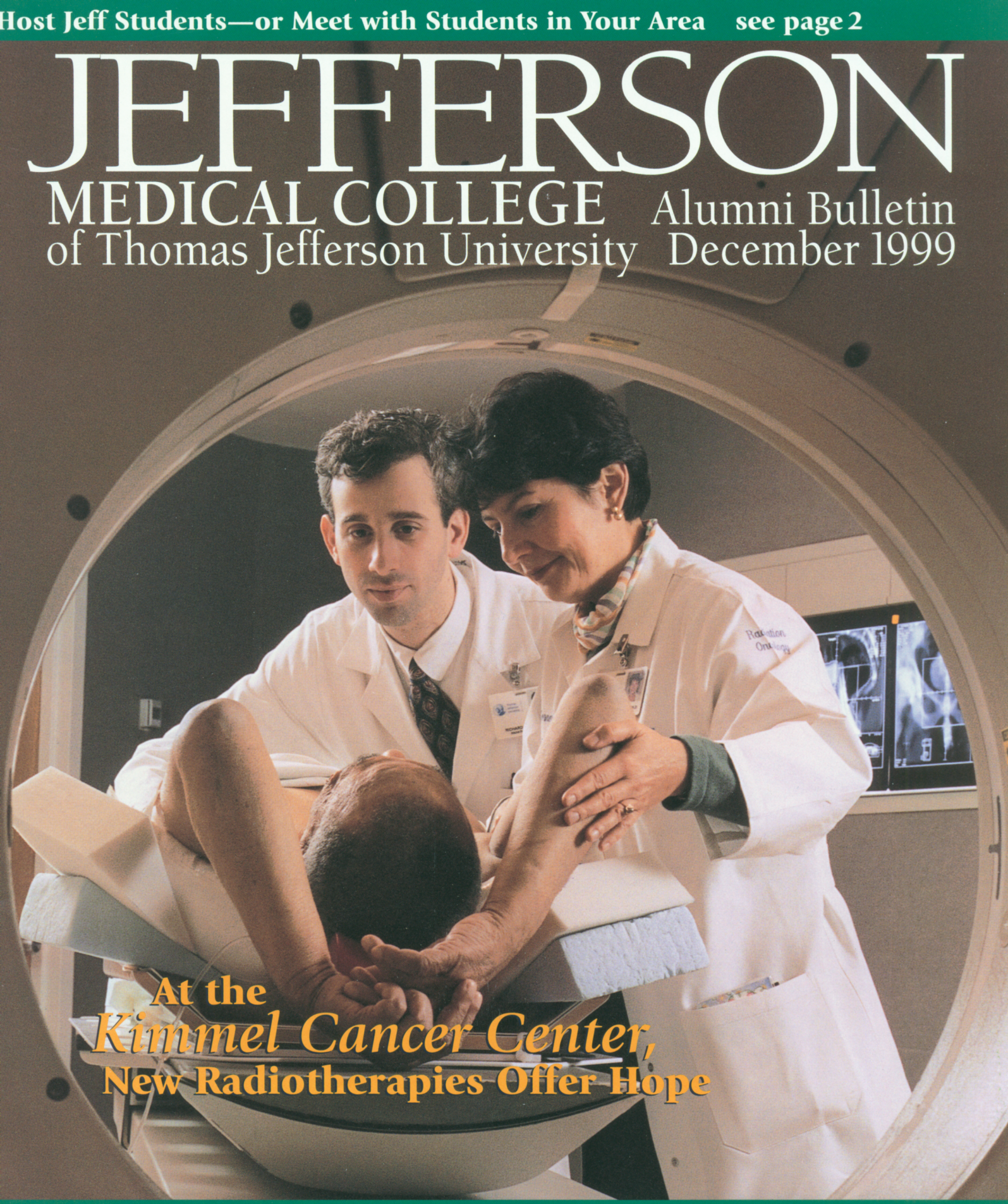
Jefferson Alumni Bulletin – Volume XLIX, Number 1, December 1999

Host Jeff Students—or Meet with Students in Your Area see page 2

JEFFERSON

MEDICAL COLLEGE

Alumni Bulletin
of Thomas Jefferson University December 1999



At the *Kimmel Cancer Center*, New Radiotherapies Offer Hope

Editor's Note: We Are Providing You the *Health Policy Newsletter*
To keep *Bulletin* readers informed about Jefferson, while containing mail costs, another publication is being shipped with the *Bulletin*. We believe you'll find that the *Health Policy Newsletter* tells you about topics that supplement those in the *Bulletin*. The *Health Policy Newsletter* is shipped quarterly, and describes health policy questions that Jefferson is studying.
Please let us know your thoughts by directing them to

Attention: Editor, *Alumni Bulletin*
Jefferson Medical College
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Phila., PA 19107
Phone: 215 955 7920
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Can You Share Your Jeff Experience with a Potential Student in Your Area?

There may be students in your geographic region who have been admitted to Jefferson Medical College, but are still in the process of deciding whether to attend Jefferson or another medical school. Benjamin Bacharach '56, Associate Dean for Alumni Relations and Acting Executive Director of the Alumni Association, urges you to talk with them about your Jefferson experience. The Alumni Office will put you in touch with specific students. Simply fill out the form below and return it to JMC Alumni Office, 1020 Locust Street M-41, Philadelphia, PA 19107.

Name _____ Class Year or Jeff Affiliation

Mailing Address _____

_____

City _____ State _____ Zip

Daytime Phone _____

I would be willing to talk with students who are deciding whether to attend Jefferson.

Can You Host a Student Interviewing or Doing a Rotation in Your Area?

Students will be contacting alumni during November, December, and January requesting housing while they are interviewing for residencies. They may be calling at other times of the year when they are doing a clinical rotation at a hospital in your area (as part of their third and fourth years of medical school). Alumni have found that this is a fun way to catch up on what's happening at Jeff, and to meet physicians-to-be who may eventually be practicing in their region. If you would be willing to host a Jefferson student, please return the form below to JMC Alumni Office, 1020 Locust Street M-41, Philadelphia, PA 19107.

Name _____ Class Year or Jeff Affiliation

Mailing Address _____

_____

City _____ State _____ Zip

Daytime Phone _____

I would be willing to host a student interviewing or doing a rotation in my area.

Upcoming Events

December 10, Friday at 8 P.M.
Free public concert by Thomas Jefferson University Choir and Orchestra
Conducted by Robert Sataloff '75
First Baptist Church, 17th and Sansom Streets

January 11, Tuesday
Alumni reception with Paul C. Brucker, M.D., President of Thomas Jefferson University, in San Diego

January 12, Wednesday
Alumni reception with Dr. Brucker in Los Angeles

January 14, Friday
Alumni reception with Dr. Brucker in Honolulu

January 19, Wednesday
Alumni reception for first year students, in Jefferson Alumni Hall

January 20–28
Cruise to the Canary Islands with Jeff alumni

January 27, Thursday
Alumni Executive Committee meeting

February 5–12
CME and Ski meeting, Telluride, Colorado

March 10, Friday
Parents Day for sophomores

March 16, Thursday
Jefferson Center for Integrative Medicine event with Andrew Weil, M.D. in Philadelphia

March 23, Thursday
Alumni Executive Committee meeting

April 15, Saturday
TJUH Women's Board Jefferson Ball in Philadelphia

April 27, Thursday
Alumni annual business meeting

May 15, Monday
Alumni reception with Dean and Senior Vice President for Academic Affairs Joseph S. Gonnella, M.D., at the Stanford Inn, Palo Alto, CA

May 16, Tuesday
Alumni reception with Dr. Gonnella in Sacramento, CA

May 17, Wednesday
Alumni reception with Dr. Gonnella in San Francisco

May 18, Thursday
Alumni reception with Dr. Gonnella in Denver

Reunion Weekend 2000
June 9, Friday, alumni banquet
June 10, Saturday, clinic presentations, reunion parties

Jefferson Medical College Alumni Bulletin
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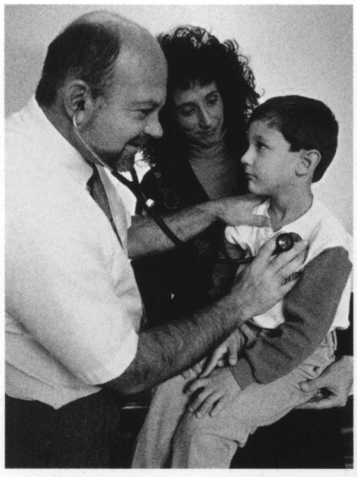


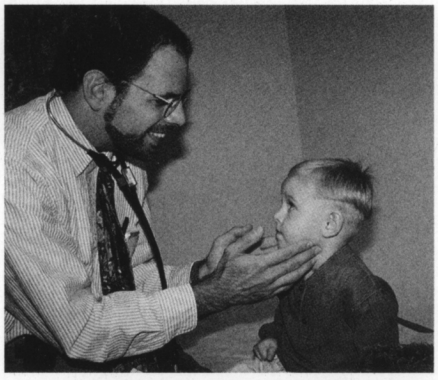
***On the cover:** Rick Hudes, M.D., Chief Resident in Radiation Oncology, and Maria Werner-Wasik, M.D., Assistant Professor, plan radiation treatment with a patient in a stereotactic body frame (see page 7).*

photo by Kelly & Massa

***On the back cover:** ophthalmologists Marlon Maus '85 and Joseph Flanagan '63 and neurosurgeon Robert Rosenwasser, M.D.—collaborators on a complex surgery (see page 33).*

Wills Eye Hosp. photo

Two products of Jefferson's Physician Shortage Area Program, James Devlin '85 (left) and Thane Turner '93 (below), see patients in rural Pennsylvania. Article on pages 27–28.



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Bringing Cancer Knowledge from the

As we embark on the 21st century, Thomas Jefferson University is deploying imaginative research and treatment against a disease that strikes one of every four Americans. Jefferson's Kimmel Cancer Center is not a single building but an integration of components, including the Bluemle Life Sciences Building, Bodine Center for Cancer Treatment, and oncology programs within various departments. Scientists and clinicians are coordinated through an infrastructure that can promote common goals and centralize data management, expediting the transfer of research results to the bedside of the sick.

Cancer research at Jefferson took a major step forward at the beginning of this decade with the recruitment of Carlo Croce, M.D., a world renowned geneticist. He oversees laboratories, primarily in the Bluemle Building, that encompass molecular biology, biochemistry, cell biology, immunology, structural biology, developmental biology, and genome mapping.

Our efforts got a tremendous boost in 1995 when Sidney Kimmel, founder and chairman of the Jones Apparel Group, a leading women's clothing manufacturer, donated $10 million for research and for an endowed fund to continue Jefferson's fight against cancer. In appreciation, the university renamed its programs the Kimmel Cancer Institute and Kimmel Cancer Center.

Also in 1995, Jefferson achieved recognition by the National Cancer Institute as a Clinical Cancer Center, one of five in Pennsylvania and approximately 60 nationwide.

The Kimmel Cancer Institute consistently merits grants approaching $50 million annually, roughly three-quarters from the National Institutes of Health and the NCI, and the rest from nonfederal grants. This extramural funding makes cancer the largest research program at Jefferson.

Unraveling Genetic Mechanisms

The investigations at the Kimmel Cancer Institute (see pages 13–15) center around oncogenes which arise in the normal genome, sometimes as a result of certain viruses. Oncogenes up-regulate cell division. If they are mutated or translocated to another site, cells may divide out of control, causing cancer.

A contributing factor can be mutations in tumor suppressor genes, which dampen the ability of cells to divide. If tumor suppressor genes mutate or are translocated, the body's normal controls against cancerous growth can be lost.

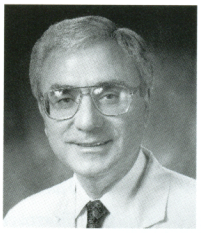
With 10 million cells dividing in the normal human body every minute, and the external environment impacting upon the body, genetic mutations inevitably occur and are passed on. Humans also have genes which can *repair* DNA damage. But if these repair genes themselves become mutated, DNA errors may go uncorrected. This increases the chance that tumors will develop as the body is exposed to carcinogenic substances that alter DNA (see page 15, lower right).

An early accomplishment by Jefferson's cancer researchers was the identification of a gene that plays a crucial role in promoting types of leukemia and lymphoma. TCL-1 is one of a group of genes implicated in the proliferation of T-cells and B-cells. Cancer occurs when the TLC-1 gene is moved out of its normal sequence on chromosome 14, and placed next to other elements known as enhancers which cause the gene to produce too much of its protein product. TCL-1 is the first gene to be implicated in low-grade leukemias such as T-cell prolymphocytic leukemia, T-cell chronic lymphocytic leukemia, and adult T-cell leukemia.

Recently, Jefferson investigators led by Dr. Croce and Professor Kay Huebner, Ph.D. discovered the FHIT gene, the second largest gene yet identified, which is involved in many common cancers (see page 13). Much work remains to be done before its mechanisms are clarified, but its significance is so great that the National Cancer Institute has called the discovery of the FHIT gene "the Rosetta Stone of cancer research."

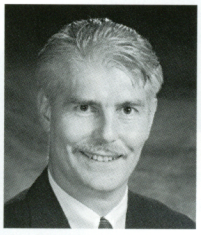
Clinical Research

Clinical cancer research at Jefferson is approaching the same level of excellence as our basic scientists. Walter Curran, M.D., Chair of Radiation Oncology at Jefferson, undertook the additional responsibility of Clinical Director of the Kimmel Cancer Center in 1997. He also serves as co-director of the lung cancer and brain tumor programs, and helped develop the Neurosensory Institute at Jefferson and Wills Eye Hospital which specializes in the use of the Gamma Knife and stereotactic radiosurgery, a super-precise radiation therapy. On the national level, Curran chairs the Radiation Therapy Oncology Group, a federally supported coalition of university departments which cooperate on clinical trials (the RTOG was in fact founded at Jefferson in the late 1960s by Dr. Simon Kramer).



Capizzi

A newly formed Translational Research Committee at the Kimmel Cancer Center promotes collaboration between Jefferson's basic and clinical scientists, and ensures that they meet all the steps required in federally funded projects. Multidisciplinary teams cross department lines to focus on such areas as hematologic malignancies and lung, genitourinary, gastrointestinal, and head and neck cancers. Jefferson is a national leader for treatment of leukemia and colorectal cancer in particular.



Boman

Robert Capizzi, M.D., the Magee Chair of the Department of Medicine, has reorganized its Division of Medical Oncology and Medical Genetics to reflect increased interest in cancer genetics. Bruce Boman, M.D., Ph.D., an expert on hereditary cancer syndromes, particularly hereditary nonpolyposis colon cancer and familial adenomatous polyposis, was recruited to head this division. Services include family pedigree analysis, individual risk assessment, genetic counseling, and genetic testing.

Phila. Inquirer/John Costello

Laboratory to the Patient

Cancer Network and Oncology Group

Jefferson is active in national coalitions conducting clinical trials, such as the Eastern Cooperative Oncology Group, the Gynecologic Oncologic Group, the Radiation Therapy Oncology Group, and the National Surgical Adjuvant Breast and Bowel Project. The number of cancer trials at Jefferson is increasing very rapidly.

Many of the institutions linked together in the Jefferson Health System have formed the Jefferson Cancer Network (JCN) to enhance clinical and translational research by increasing the number of individuals enrolled in these trials. Patients at any JCN member can easily become enrolled in a wide array of trials, which offer patients the latest therapies as soon as they have been developed.

Currently the network includes Jefferson, Atlantic City Medical Center, Bryn Mawr Hospital, duPont Hospital for Children, Albert Einstein Medical Center, Frankford Hospital, Grand View Hospital, Lankenau Hospital, Mercy Community Hospital, Mercy Fitzgerald Hospital, Mercy Hospital of Philadelphia, Methodist Hospital, Riddle Memorial Hospital, Underwood-Memorial Hospital, Wills Eye Hospital, and the Kimmel Cancer Center radiation oncology programs at Chestnut Hill and Lower Bucks Hospitals.

Curran in the radiation facility

Radiation therapists prepare a patient.

With approximately 20,000 new cancer patients diagnosed within the Jefferson Cancer Network each year, Dr. Capizzi believes the Kimmel Center now has the critical mass needed to run conclusive clinical trials within the JCN itself. The Kimmel Center and the network provide sufficient infrastructure, technology, and numbers of patients to be a self-contained trials group—the Jefferson Oncology Group—along the lines of the Eastern Cooperative Oncology Group.

The JOG now has a common Institutional Review Board with approval authority over all trials involving its members. And the member institutions are being coordinated so as to have a single signature contracting ability with pharmaceutical industry sponsors.

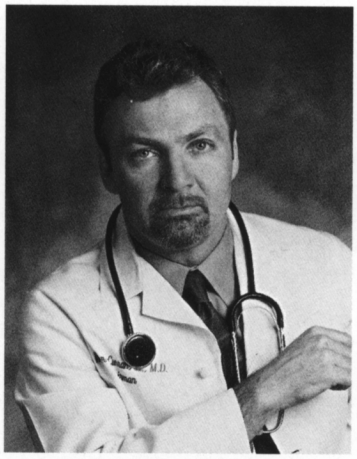
Back on the university's Center City campus, it is likely that in the year 2002, many of the scientists and clinicians of the Kimmel Cancer Center will move into a large new structure of their own. It would include outpatient facilities for ambulatory cancer patients, as well as research labs. The clinical side of the building would be laid out so as to encourage interaction between clinicians and investigators dealing with the same types of pathology.

The new cancer building would mean a major expansion of total lab space, enabling Jefferson to recruit more investigators and obtain significantly more federal grant money than at present. Jefferson will become even more effective at better ways to predict, diagnose, and fight a devastating disease.

Increasing the Effectiveness of Radio

Nearly two thirds of people diagnosed with cancer today will receive radiation as part of their therapy. Incremental improvements in technology over the last century have culminated in what Chair of Radiation Oncology Walter J. Curran Jr., M.D. calls "revolutionary improvements over the last decade." At Jefferson's Kimmel Cancer Center, that revolution can be seen at the 50,000 square foot Bodine Center for Cancer Treatment, opened 12 years ago not only to offer the best, but also to ensure the continual development of new radiation therapy technologies.

What has changed in recent years, said Curran, is that radiation oncologists and other cancer specialists have learned that the best cancer treatment often incorporates multiple specialties and modalities. "With trained oncology nurses, with pharmacists, with psychologists and social workers, the Bodine Center was one of the first centers in the Philadelphia area to recognize the need for multispecialty collaboration in the management of cancer patients," said Curran. "And we still serve as a model of that." Radiotherapy may be used in conjunction with surgery or chemotherapy to achieve more complete tumor elimination or to control metastasis, and in some cases it can also be used in place of surgery when the goal is to preserve organ function, such as in the case of cancers of the throat, larynx, esophagus, prostate, and breast.



Curran

And even when a cure is not the goal, palliative radiotherapy may provide significant benefit to patients with cancers that are locally advanced or that have spread to the bone or the brain. Said Curran, "Probably about half of patients who have incurable cancer benefit from radiotherapy in terms of quality of life and pain control."

The approach that Jefferson uses incorporates different technologies to provide image-based treatment planning and delivery. That typically includes techniques that immobilize the patient to the greatest degree possible; imaging modalities such as spiral CT scanning, which provides high resolution images; and planning tools that calculate the most effective way to deliver the right dose of ionizing radiation to the target while sparing normal tissues.

Precision Targeting

For the more than 200,000 men each year diagnosed with prostate cancer, all of the treatment options have risks. Surgery, while offering the potential of complete removal of the tumor, too often results in damage to the surrounding nerves, sometimes resulting in impotence and incontinence. Radiotherapy, in contrast, offers an increased likelihood of retaining sexual potency. Yet irradiating prostate tumors buried deep in the pelvis places nearby sensitive structures such as the rectum and bladder at risk of radiation-induced damage. In order for radiation therapy to be an acceptable alternative in prostate cancer and many other forms of cancer, techniques have been developed that concentrate the delivery of ionizing radiation to the tumor itself, while limiting radiation exposure of the surrounding tissue.

The traditional approach to treatment planning, called conformal 3-D treatment, is to look at the cross-sectional CT image of the tumor and arrange the fields to miss healthy structures as much as possible, and then to irradiate the tumor from a number of different directions. "That works rather well in concentrating the radiation in the target area and sparing the critical structures," said James M. Galvin, D.Sc., Professor and Director of the Medical Physics Division in the Department of Radiation Oncology. "We use our bag of tricks to get a good dose distribution." These tricks include various techniques that weight the fields differently and modify them with absorbers placed in the beam.

An alternative to the traditional approach to treatment planning, called inverse planning, is now being used at Jefferson. Employing a delivery system called "Peacock," which was developed by Nomos Corporation of Sewickley, Pennsylvania, it allows the radiation oncologist to start with what is the ideal dose distribution and to work backward from that point to determine the appropriate configuration of radiation delivery. "It's a total reversal of the approach," said Curran. "Normally we think of the fields and base the dose strictly on that. Here we think of the dose and then use the treatment planning technology to determine the delivery process that will give us that dose."

The Peacock system delivers what is called intensity modulated radiation therapy (IMRT), using an approach known as "layered therapy," said Maria Werner-Wasik, M.D., Assistant Professor of Radiation Oncology. A special crane moves across the treatment table, delivering many small radiation beams of varying intensity. This allows the physician to modify the delivery of radiation to conform to the shape of the tumor, even if it is an irregular shape, and to get uniform levels of radiation to tumors that vary in thickness and that have hard-to-reach margins, while at the same time avoiding normal tissue. "It's the radiation oncologist's dream to be able to do this," said Werner-Wasik. By delivering radiation more precisely, Peacock allows the physician to deliver higher levels of radiation without harming normal tissue, thus increasing the likelihood of cure.

In addition, physicians may be able to provide a second course of radiotherapy when necessary. "Peacock may allow us in some cases to treat tumors that recur after initial courses of radiation," said Werner-Wasik.

The key to inverse planning is computation, according to Galvin. "You give the computer very detailed geometric information about the tumor you're trying to treat, and also about the critical body structures in the vicinity," he said. "Then you ask the computer to determine the ideal combination of beams and angles that will deliver a homogeneous dose of radiation to the various areas of the tumor regardless of its shape. And you give the computer the flexibility of varying the beam intensity at will."

herapies

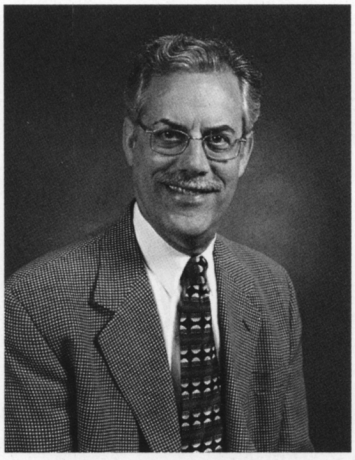
The idea of inverse planning was developed in the 1980s and '90s, before there were convenient ways available for modulating the beam intensity point for point. "It was a technique in search of a technology to implement it," said Galvin. But in the early '90s, he and others introduced a new field-shaping device called the multi-leaf collimator, with which one can obtain any irregularly shaped field using a computer to drive fingers in and out of the radiation beam. "It occurred to me that if you shaped different fields and then stacked them up, you could build up any intensity pattern. So with the introduction of the multi-leaf collimator, we now had a tool to modulate the intensity of the beam so we could deliver these inverse plans."

This allowed radiation treatments to be shaped to irregular tumor volumes. "We could now shape the dose to a horseshoe-shaped tumor with a critical structure right in the center of it. We couldn't do that in the past."

The problem with inverse planning is that the computer sometimes comes up with very elaborate solutions: elegant dose distributions that are difficult to deliver because of various compromises that were called for during the planning process. For example, when the tumor surrounds a critical structure, the delivery of sophisticated distributions of radiation sometimes requires sacrificing dose homogeneity.

"So here at Jefferson we asked, well, if we're going to change the rules of treatment planning so dramatically, then why not go back to the traditional techniques and see how they perform under this new set of rules," said Galvin. This has led to the development of a new approach, dubbed forward planning as opposed to inverse planning. "We still have made it an intensity modulated delivery, it's just that whereas we had inverse planning coupled with IMRT, we're now using traditional techniques combined with IMRT. We have fields within fields and we still stack fields, but we use our past experience to say what those fields within fields should look like." While optimization of the plan is still left to the computer, said Galvin, "We give the computer more information going in, and tell the computer that we think that these fields are the ones it should be looking at. 'Now, computer, you optimize it.' "

Galvin explained that while inverse planning may be the wave of the future, the forward planning technique being developed at Jefferson is more suited to the technology that is currently available. Eventually, there may be a melding of the two approaches, he said. "The terminology will change—it will become simply computerized planning."



Galvin

Holding Still

Another device that maximizes delivery of radiation to the target and not to surrounding tissue is the stereotactic body frame (see front cover photo), a piece of equipment with calibrating devices built into it that allow the precise localization of body structures in three dimensions during a CT or MRI scan. Historically, patients simply lay on a table while receiving radiation therapy. Then, plastic molds were introduced which kept people from rolling around during treatment. "But if you want to give high doses of radiation to critical areas in the body, we've concluded that you really need to have more rigid immobilization," said Curran. Jefferson was one of the first American sites to use the stereotactic body frame to immobilize patients during radiation therapy, and remains the only one in the Delaware Valley.

The device *looks* barbaric, Curran remarks, resembling the kind of box a magician uses when he cuts a woman in half. The patient is placed in it prior to a CT scan. Images produced from this scan show the location of the tumor relative to fixed points in space provided by the calibrating device. Then, while the patient's positioning is maintained by the box, he is moved to the treatment area where radiation is delivered relative to those same fixed calibration points.

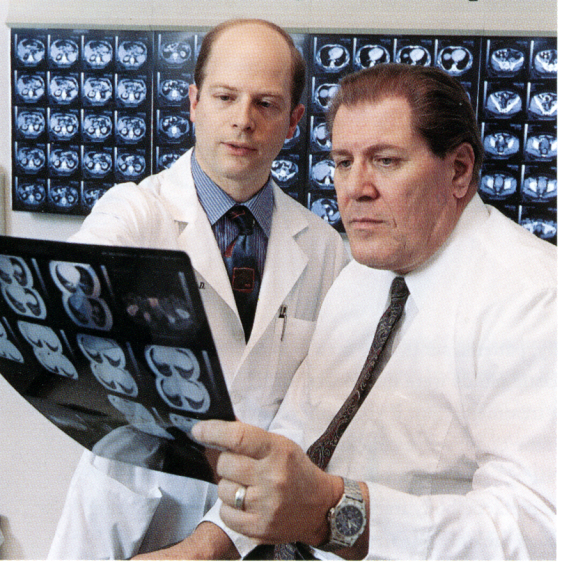
The difficulty comes in transferring the patient from the CT scanner to the treatment area. Jefferson staff, however, have developed a unique transferring technique in which the patient can be moved off the CT scanner, down the hall, and into the treatment unit without being jostled.

The Jefferson team uses a modified hospital gurney to facilitate this transfer. The gurney allows the staff to slide the patient smoothly off the CT couch, onto the transfer couch, and then onto the treatment table. Then, using marks on the patient and on the frame, the radiation fields are delivered to an exact position within the patient's body.

"The importance of doing this is that we can now decrease the margins," Galvin explained. Margins refer to the area surrounding the tumor that may be irradiated during the treatment. Less precise localization of the tumor or more uncertainty about the patient's exact position relative to the images means that those margins must be increased in order to ensure adequate delivery of radiation to the tumor. "We're trying to minimize the size of the margins so that we are irradiating less of the healthy tissue, while still getting all of the tumor."

New Approaches Make Radiotherapy Better

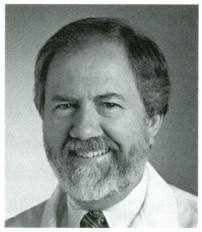
For all of these new technologies, rigorous evaluation of the results is the key to ensuring progress in the search for better treatments. Jefferson patients benefit from participation in clinical trials of protocols developed all over the world, due to the university's involvement in federally funded cooperative oncology groups such as the Radiation Therapy Oncology Group, which Curran currently chairs. These clinical trials are essential for the continued evolution of therapies that will yield better outcomes and fewer side effects.



Dr. Dicker explains a set of CT scans.

Right: Dr. Leeper

Below: A radiation therapist prepares a patient for treatment. The mask protects areas of the face.



biochemically quite different from those of radiation and drugs, Leeper explained. First, heat denaturizes proteins, in the same way that when you cook an egg, the protein in the white changes from a clear, slippery liquid to a white solid mass. By denaturing and changing the structure of proteins in cells, heat inhibits the repair of the tumor's damage from radiation and chemotherapeutic agents.

Second, through other chemical and biochemical processes, heat makes the tumor's DNA more reactive with drugs and radiation, increasing the effectiveness of the drugs and radiation. And what makes the combination of heat and radio- or chemotherapy even more desirable, is that the cells in tumors that are sensitive

For example, clinical trials recently resulted in preliminary FDA approval for an agent called amifostine, which protects against radiation-induced dry mouth, or xerostomia. Werner-Wasik with Robert Capizzi, M.D., the Magee Chair of the Department of Medicine, conducted this trial at Jefferson, and Werner-Wasik continues to see if this agent might be useful as a protectant against chemo- and radiation-induced esophagitis in lung cancer patients.

Adam Dicker, M.D., Ph.D, Assistant Professor of Radiation Oncology, meanwhile has been working with a technique called brachytherapy, in which radioactive seeds are implanted into early stage prostate tumors. Dicker collaborates with Professor Frank M. Waterman, Ph.D. The idea behind brachytherapy is that higher doses of radiation can be delivered directly to the tumor, without affecting adjacent tissues. Long term studies of the effectiveness of brachytherapy are underway, as is research to improve the methodology.

Werner-Wasik discusses a procedure, along with visiting fellow Marisa LoBao, M.D.

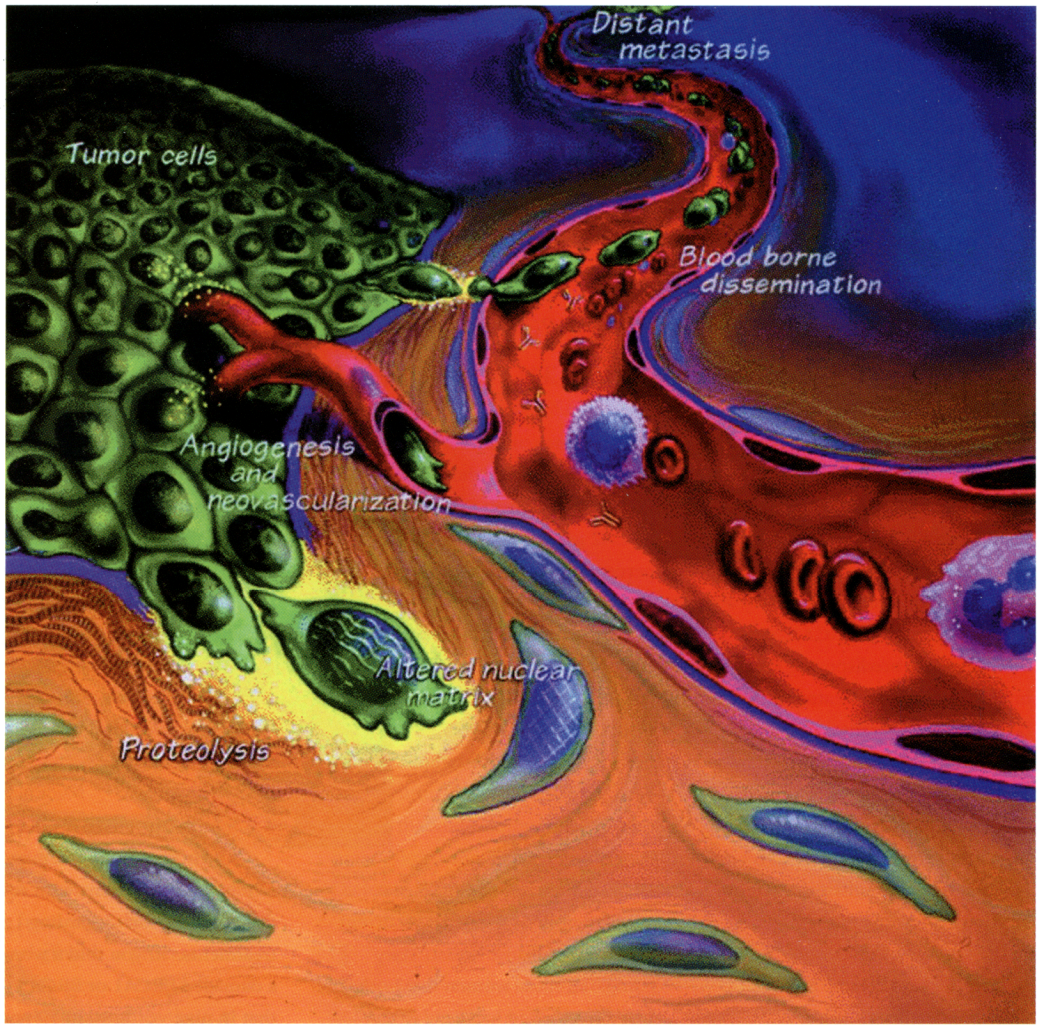
Adjuvant Therapies

Many of the most promising developments in radiation oncology involve the use of adjunctive therapies that augment the standard treatment. One that has undergone extensive development at Jefferson is hyperthermia, or applying heat to the tumor. In the past two decades, said Dennis Leeper, Ph.D., Professor of Radiation Oncology, about 700 patients have received hyperthermia treatments at Jefferson.

Hyperthermia increases the effectiveness of radiation therapy through two pathways: by killing cells directly and by making cells more sensitive to radiation-induced damage. The mechanisms of hyperthermia's effects are

to heat are resistant to radiation and to drugs. In addition, physiologic factors inherent in tumors, such as chaotic blood flow and increased acidity, make tumor cells particularly sensitive to hyperthermia. "So you have a complementation of the interaction, as well as the heat sensitizing cells to these agents," said Leeper.

According to six randomized clinical trials, the net effect of this complementation and sensitization is a demonstrated benefit for patients who receive hyperthermia plus radiation over radiation alone for head and neck cancers, melanoma, breast cancer, brain gliomas, and tumors of the cervix and bladder. "The addition of hyperthermia to the standard course of radiation therapy in most of these studies has approximately doubled the response rate and doubled the local control rate; that is, freedom from cancer at three to five years out," said Leeper. "And three studies have also shown an improvement in survival."

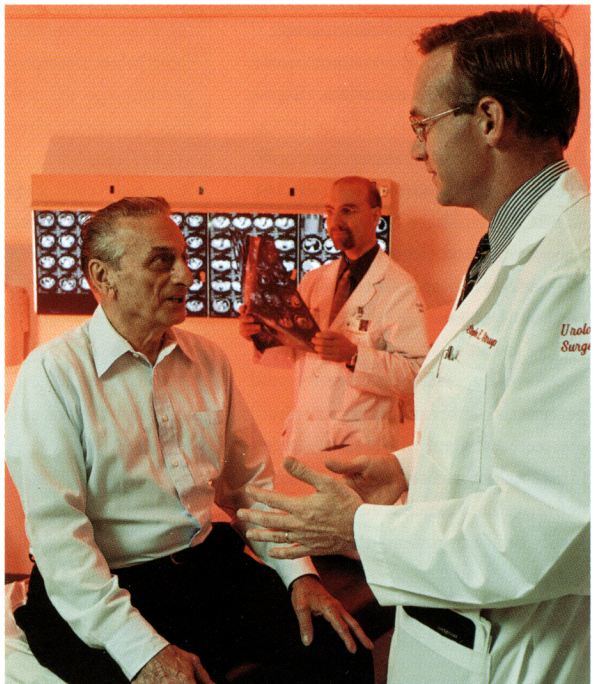


Yet despite the proven benefit of hyperthermia, its use as an adjunctive therapy for cancer remains limited for several reasons. First, treatments are lengthy, labor intensive, and expensive. And an even greater problem has been the lack of a good noninvasive thermometry system that would allow physicians to know exactly where and how much heat is being delivered. This has been especially problematic with tumors that are not near the surface, for instance in the cervix or colon. Leeper said that in the past two years, researchers have made significant advances in this area by using MRI to image temperature. "It's a technology that we're just about ready to apply."

Hyperthermia is also being investigated as an adjunct to gene therapy, he added, using genes that confer sensitivity to heat to regulate the expression of other genes that might have therapeutic effects, for example, toxins or immunomodulators.

Another new area of cancer research that has generated great excitement in recent years and that may be used in conjunction with radiotherapy is the use of angiogenesis inhibitors. These are drugs that block the proliferation of new blood vessels, a process known as angiogenesis ***(see graphic above)***. In order for tumors

continued on page 11



Radiation after Surgery Helps Prostate Cancer Patients Stay Disease-free

Researchers at Jefferson have discovered that nearly 90 percent of high-risk prostate cancer patients who received radiation therapy after surgery did not have cancer five years later. Only 55 percent of those who didn't receive the treatment did not have any signs of cancer.

"The understanding before was that adding radiation therapy did not reduce the rate of cancer progression, didn't help long-term survival, and probably wasn't justifiable," says Richard Valicenti, M.D., Assistant Professor of Radiation Oncology. "Instead, these results suggest a real benefit from postoperative radiation." The researchers reported their findings in the August issue of the *International Journal of Radiation Oncology Biology and Physics.*

continued on page 10

Left: a weekly genitourinary clinic takes a multidisciplinary approach. Stephen Strup U'94, Assistant Professor of Urology (right) and Dr. Valicenti of Radiation Oncology together review treatment options with a patient. These could include both surgery and radiation for optimal benefit.

Women with Inherited Breast Cancer Gene Are at Greater Risk for Recurrence and New Tumors

For many women under 40 with breast cancer, surgery to remove the lump and accompanying radiation seem a good way to get rid of the disease yet preserve the natural breast. But for women who carry a damaged version of BRCA1 or BRCA2, genes predisposing them to breast cancer, such treatment may not be enough. Researchers at Jefferson have found that such women have a greater risk of either relapsing or developing new tumors years later than those women who receive a lumpectomy and radiation therapy but don't carry one of these genes.

As a result, says Bruce Turner, M.D., Ph.D., Assistant Professor of Radiation Oncology, who led the work, women and physicians may want to rethink their treatment options. "Our findings suggest that a woman who has a mutation in BRCA1 or BRCA2 who is treated with breast-conserving therapy not only has a high risk of local recurrence—40 percent according to our study—but also a high risk of developing cancer in the other breast as well," Dr. Turner says.

"Our data imply that breast-conserving therapy may not be the optimal treatment for breast cancer patients with BRCA1 or BRCA2 mutations who want to reduce the risk of locally recurrent breast cancer."

Dr. Turner and colleagues at Yale University and Myriad Genetics reported their findings in the October issue of the *Journal of Clinical Oncology*.

Of 170,000 new breast cancer cases a year in U.S. women, about 10 percent of the women are under 40. Roughly 10 to 15 percent of those women (2,000) carry an altered BRCA1 or BRCA2 gene, and about 70 to 80 percent develop breast cancer.

Turner

Dr. Turner and his coworkers looked at the frequency of alterations in BRCA1 and BRCA2 in 52 breast cancer patients who, between 1973 and 1994, were treated with breast-conserving lumpectomy and radiation, and who subsequently developed a recurrent cancer in the same breast. They compared these women to 52 other women who had localized breast cancer and were treated similarly but did not experience recurrent disease.

The researchers found that eight, or 15 percent, of the 52 women who had further breast cancer also carried a damaged BRCA1 or BRCA2 gene. In women 40 or under with recurrent breast cancer, six of 15, or 40 percent, had a damaged inherited BRCA1 or BRCA2 gene. In contrast, only one of 15 women in the comparison group who did not have any recurrent cancers carried the bad gene.

The scientists also found that it took longer—an average of about eight years—for women with an altered BRCA1 or BRCA2 gene to relapse than it did women without the damaged gene (slightly less than five years on average). They then carefully examined the tumors using molecular and histologic analysis, thinking these were old cancers that had returned. Instead, they found that some of the tumors were actually completely new breast cancers. The new cancers took an average of 8.5 years to develop.

"If this study is validated with a larger prospective study, it may suggest that BRCA1 or BRCA2 testing may be reasonable to determine optimal breast cancer treatment—either breast-conserving therapy, or mastectomy for younger women with family histories of breast or ovarian cancer," Dr. Turner says.

The study results may present women and their physicians with some difficult decisions regarding treatments. "If you told a woman with a damaged BRCA1 or BRCA2 gene that in nine years, 40 to 50 percent of patients like her are going to have a new breast cancer, and may need a mastectomy, then you'd have to present alternatives to her: would she prefer the lumpectomy and seven weeks of radiation, or would she rather have the mastectomy now and reduce the risk of recurrent disease?"

One problem with recurring cancer is the threat that the disease may spread. While breast-conserving therapy may be curative for many women, some women who develop recurrent breast cancer also develop metastatic disease.

Dr. Turner says that researchers now need to "look at patients with BRCA1 or BRCA2 who have had a mastectomy and consider the frequency of chest-wall relapse and metastatic disease.

"Presumably, removing 90 to 95 percent of the breast cancer cells by mastectomy significantly reduces the future risk of breast cancer. But more definitive data is needed before we can justify this recommendation."

Radiation and Prostate, *from page 9*

Prostate cancer tends to be a slow growing disease that men frequently die *with*, not *from*. Doctors often question whether surgery or radiation provide any real benefit for the older patient.

Since 1990, the reported new cases of prostate cancer have more than tripled, from fewer than 100,000 annually to more than 300,000, owing to better detection and greater public awareness. More than 60,000 men a year receive radiation therapy for localized disease.

Dr. Valicenti and his Jefferson colleagues followed 149 men with localized cancer that had not spread beyond the prostate, who were considered high-risk for cancer recurrence after surgery. Fifty-two men were given radiation therapy three to six months after surgery; the others received no radiation.

The scientists carefully matched the two groups according to factors that predict whether a cancer will return, settling on 72 patients in 36 matched pairs. They then examined the patients every three to six months and tested their blood for prostate-specific antigen. Rising PSA indicates a returning cancer.

After five years, 89 percent of the matched patients who had received radiation after surgery had no detectable PSA level, compared to only 55 percent of those who didn't get radiation.

Valicenti and his colleagues hope to conduct a multisite national study to see if these results can be repeated with a larger group.

Clinical Trial of Radiation and Thalidomide for Brain Tumors

Researchers at Jefferson and 14 other sites around the country are enrolling patients into a National Cancer Institute sponsored clinical trial examining the effects of radiation and thalidomide in treating glioblastoma multiforme, a deadly brain cancer. The Phase Two trial, conducted by the nationwide clinical trial cooperative known as the Radiation Therapy Oncology Group, in collaboration with Celgene Corporation of Warren, New Jersey, aims to determine the drug's safety and effectiveness in extending patients' lives. The study, which will last into the year 2000, involves approximately 80 patients.

Glioblastoma multiforme is the deadliest type of brain tumor. Although any of the brain's cells can turn malignant, glioblastoma multiforme, a tumor of the glial cells, is the most common and the most malignant. The tumor has a tendency to infiltrate surrounding tissue and is commonly associated with promoting blood vessel growth, bleeding, and tissue death. In the United States, the disease strikes approximately 9,000 individuals, with a median survival time of about 12 months following diagnosis.

"This combination treatment may be an important step in fighting a normally intractable illness that resists all other therapies," says Walter J. Curran Jr., M.D., Chair of the Radiation Therapy Oncology Group and Clinical Director of Jefferson's Kimmel Cancer Center.

Curran points out that the RTOG study "is the first trial of its kind to look at radiation and thalidomide in treating any cancer."

While surgery and radiation are the standard treatments for glioblastoma, their effects are usually temporary. Chemotherapy has marginal value, failing to reach areas in the brain to which the cancer has spread, says Curran, "which is why we have looked for alternatives." The study will include patients who have not previously undergone radiation therapy or chemotherapy.

Thalidomide works by cutting off the blood supply to tumors. Tumor cells are frequently able to engineer new vessel growth, a process called angiogenesis (see graphic on page 9), which promotes the cancer's spread. Thalidomide inhibits a growth factor that tumor cells need in order to sprout new vessels. Thalidomide won't knock out the cancer cells, but may prevent them from spreading by cutting off nutrients which they need in order to multiply. Because the drug targets rapidly dividing cells, it is not expected to cut off the blood supply to most normal cells.

If thalidomide works, it would be a complement to other strategies like surgery, chemotherapy, and radiation. "To control brain tumors effectively, we need a whole host of services," Curran explains.

In the 1960s, thalidomide, originally intended to treat morning sickness, was banned around the world after causing thousands of babies to be born either without limbs or with flipper-like arms and legs. In recent years, however, the drug has been used to treat leprosy, cancer, AIDS, and other diseases.

Adjuvant Therapies, *from page 9*

to grow, they require new blood vessels to deliver oxygen and nutrients. By blocking the formation of new vessels, researchers believe they may be able to starve the tumor. Since angiogenesis inhibitors are cytostatic (preventing the growth of a tumor) rather than cytotoxic (killing the tumor), they will most likely be used in conjunction with chemotherapy or radiation therapy as a cancer treatment.

One of the anti-angiogenesis agents being tested at Jefferson is thalidomide, the same drug that was widely given, with disastrous results, to pregnant women in the 1950s as a treatment for morning sickness. Thalidomide was withdrawn from the market when it was shown to cause severe birth defects. But in 1994, researchers demonstrated that the very properties that damaged the developing fetus, that is, inhibition of new vessel growth, could be used therapeutically to starve tissues such as tumors. An RTOG-sponsored clinical trial of thalidomide used in conjunction with radiotherapy as a treatment for brain glioma is now underway (see article at left), with Jefferson's Adam Dicker chairing the correlative studies section of the trial.

Dicker explained that angiogenesis, as measured by the density of microvessels (the MVD) in a given area, has been shown in many studies to correlate with tumor extent, aggressiveness, decreased survival, and lymph node metastases. A landmark paper in 1991 showed that in a study of women with breast cancer, all patients with microvessel counts over a certain threshold developed metastases. "This was the precedent for thinking, well, if there's increased angiogenesis in patients with more advanced disease, then presumably if you impact on the angiogenesis you might impact on the overall progression of the disease," said Dicker, who is collaborating on research with George Iliakis, Ph.D., Professor and Director of the Radiobiology Division.

Another reason for the excitement about angiogenesis inhibitors is that preclinical data indicates little likelihood that tumors will develop resistance to these agents. "It takes a long time for these anti-angiogenesis agents to have an effect," Dicker notes, "but they have a very durable length of response."

While Curran and the faculty in Radiation Oncology are proud of the basic, translational, and clinical research programs, Curran stresses that patient care is the top priority. To this end, the Kimmel Cancer Center recently celebrated the addition of two new partners, the radiation oncology center at Frankford Hospital, and the Jefferson radiation oncology center at Riddle Memorial Hospital in Delaware County. These facilities will help increase the number of newly referred patients seen through the Jefferson system to about 3,500 per year. Many of these patients are seen in multidisciplinary programs and benefit from the collaborations of researchers and clinicians in multiple specialties.

"We're devoted to offering state of the art therapy while at the same time critically evaluating its potential benefit to patients," said Curran. "Just because it's new technology doesn't mean it's better." —*Lisa J. Bain*

Continuing Recognition for Jefferson's Specialists

Jefferson's many experts on the causes and treatment of cancer continue to earn national recognition. A few highlights this past year:

AACR-Pezcoller Award for Cancer Research

Celebrated geneticist Carlo M. Croce, M.D., Director of Jefferson's Kimmel Cancer Center, has added the AACR-Pezcoller Award to his long list of achievements. The award is given by the American Association for Cancer Research to a scientist who has made a major discovery in cancer research.

Dr. Croce, who also chairs Jefferson's Department of Microbiology and Immunology, has been a pioneer in understanding the genetic causes of cancer. The AACR noted that his "contributions have not only greatly extended our knowledge of cancer genetics, but they also constitute the basis for potential breakthroughs in gene therapy for human cancer."

Among his accomplishments, Dr. Croce has explained the roles of chromosome alterations in human leukemias and lymphomas and identified several genes involved in blood cancers. A genetic profile of these genes is already being used in clinical settings to detect remaining disease in patients following treatment.

More specifically, Croce described the molecular-genetic events that result in Burkitt's lymphoma, follicular lymphoma, and lymphomas in AIDS patients. He and his team have also isolated and named the ALL-1 gene, which is critical to the development of leukemias and lymphomas. Dr. Croce and Dr. Kay Huebner identified and cloned the tumor suppressor gene FHIT, which continues to yield vital information on the development of cancer (see article on facing page).

A member of the National Academy of Sciences, Croce has won numerous honors including two Outstanding Investigator Awards from the National Cancer Institute, the General Motors Research Foundation Charles S. Mott Prize, the Pasarow Award, and the John Scott Award.

Nation's Top Cancer Specialists According to Good Housekeeping

Jefferson faculty Walter J. Curran Jr., M.D., Robert D. Fry, M.D., and Gordon Schwartz, M.D. are among the nation's top 318 cancer specialists for women, according to the 1999 study by *Good Housekeeping* magazine. The guide lists the most respected experts for lung, breast, and colon disease.

Good Housekeeping's editors made their selections based on nominations from nearly 300 department chairs and section chiefs at major medical centers around the United States. These physicians were asked to select "the specialists who provide the most expert treatment and who are the leading clinicians for lung, breast, and colon cancer in women."

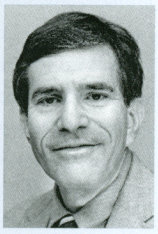
As Clinical Director of Jefferson's Kimmel Cancer Center, Dr. Curran oversees a range of the most advanced patient services in every specialty dealing with cancer. The Kimmel Center also acts as the point of entry for patients taking part in clinical trials conducted by Jefferson cancer specialists. Curran is also Chair of Radiation Oncology at Jefferson, and heads the Radiation Therapy Oncology Group, a consortium of more than 200 institutions in the U.S. and Canada aligned to conduct clinical trials.

Robert Fry, M.D., Director of Colon and Rectal Surgery at Jefferson, has written extensively on the care of gastrointestinal disorders and cancers, especially those affecting the colon and rectum. He has collaborated on more than 20 books and book chapters. Dr. Fry continues Jefferson's unparalleled success in managing colorectal cancer, and is also pursuing studies of the mechanism and treatment of inflammatory bowel disease. He is a Director of both the American Board of Colon and Rectal Surgery and the American Board of Surgery.

Gordon F. Schwartz, M.D., Professor of Surgery at Jefferson, is a world-renowned breast cancer surgeon. He serves on the editorial boards of *Cancer, Seminars in Breast Disease, The Breast Journal, International Journal of the Breast,* and *Mammary Pathology,* and is a member of the National Institutes of Health Reviewers Reserve.

Dr. Schwartz also heads an international group of breast cancer experts who meet at Jefferson each year to discuss the diagnosis and treatment of Ductal Carcinoma in Situ (DCIS), a controversial malignancy found in the breast. In recent years, the group designed a system for classifying DCIS, a first step toward improving treatment for this type of early breast cancer. DCIS currently represents 20 to 25 percent of all breast cancers diagnosed.

President of the Society of Breast Imaging



Stephen Feig, M.D., Professor of Radiology at Jefferson and Director of the Breast Imaging Center, is now the national President of the Society of Breast Imaging. A nationally recognized radiologist who specializes in breast cancer detection and diagnosis, Dr. Feig was one of the founding members of SBI in 1985. The society comprises more than 2,000 radiologists.

Feig is the author or coauthor of more than 300 papers and chapters and 15 books on breast imaging and breast cancer detection. His research has covered benefits, risks, and costs of screening mammography, especially for women ages 40 to 49, the technical quality of mammography, and digital mammography.

Dr. Feig is also a member of the American College of Radiology Breast Task Force and chairs the ACR's Mammography Accreditation Committee and the Ad Hoc Committee on Mammography Screening Guidelines. He holds leadership positions in the National Council on Radiation Protection and Measurements and the American Board of Radiology. He is Editor of the journal *Seminars in Breast Disease* and serves on the editorial board of *Radiology*.

Molecular Pathways of Apoptosis

By detailing the precise molecular pathways of apoptosis, or programmed cell death, scientists at Jefferson are edging closer to new therapies against cancer, Alzheimer's disease, and Parkinson's disease.

In the June 10 issue of the journal *Nature,* Emad Alnemri, Ph.D., Associate Professor of Microbiology and Immunology at Jefferson, in collaboration with Yigong Shi, Ph.D. of Princeton University, described the workings of caspase-9, an enzyme that is crucial to apoptosis. They have elucidated part of the cascade of cellular events leading to activation of this enzyme in apoptosis.

"Labs across the country are trying to develop drugs that inhibit caspases, in order to fight neurodegenerative diseases and other diseases in which apoptosis is involved," points out Dr. Alnemri. Understanding the apoptotic pathway and each protein's role in the cell-to-cell communication process will open the way to developing drugs.

Apoptosis is a fundamental biological process that is vital to cell differentiation and normal development. In human embryos, for example, apoptosis creates fingers from mitt-like hands. It occurs during normal aging, and sometimes during irreversible cell injury from radiation or other poisons. Scientists believe that apoptosis gone awry underlies cancer, neurodegenerative diseases such as Alzheimer's and Parkinson's, and autoimmune diseases such as lupus.

Apoptosis has received great attention in the popular press in recent years since scientists discovered that part of the reason cancer cells grow with abandon is that they lose the directive to die at a preset time.

Alnemri is studying how various molecules affect the process, particularly what triggers it to begin with. He focuses on caspases, a family of 14 proteases (enzymes that degrade critical cellular proteins). Seven of these are known to be involved in apoptosis. Alnemri and his coworkers discovered many of the caspases themselves.

In the *Nature* paper, the researchers concentrated on better understanding the chemical "recognition complex," or precise binding region, between caspase-9 and Apaf-1 (apoptotic protease activating factor one), a protein that helps regulate apoptosis. "They bind to each other—we published that in an earlier journal article—but no one knew how. The crystal structure of the binding complex was unclear," Alnemri explains. "We wanted to know which amino acids were involved."

The scientists overexpressed and crystallized the actual pieces of Apaf-1 and caspase-9 that bind to each other. Then they used x-ray crystallography to analyze the chemical structure of the recognition complex. They showed how mutation of even a single critical amino acid within the recognition complex can affect the binding between the two proteins.

Dr. Alnemri contends that a key to halting the disease processes involved in degenerative diseases such as Alzheimer's may lie in this attachment. "If we find a molecule that can disrupt these two proteins from binding, it could be used in a drug. For example, a compound that could bind to the surface of the caspase might block the apoptotic pathway and prevent the process from occurring."

Creating such drugs would involve developing peptides that mimic the chemical "recognition sequence" on the two crystal structures of caspase-9 and Apaf-1, and then testing to see if they indeed disrupt apoptosis. It would be a first: no caspase-based drugs currently exist that block apoptosis in this manner.

Further Evidence Links FHIT Damage with Breast Cancer

Scientists at Jefferson, working with the University Hospital of Iceland and the National Human Genome Research Institute in Bethesda, Maryland, have found further evidence linking damage to the tumor suppressor gene FHIT to the development of breast cancer.

In a study of 92 Icelandic women, researchers led by Kay Huebner, Ph.D., Professor of Microbiology and Immunology at Jefferson, showed reduced levels of Fhit, the protein for which FHIT encodes, both in women with sporadic breast cancer and in those with hereditary breast cancer who carry a BRCA2 mutation, a gene predisposing them to develop the disease. Among the 58 sporadic and 34 BRCA2-associated breast cancers, Dr. Huebner's team reported a "significant association" between damage to the FHIT gene at its most fragile area and a reduced expression of the Fhit protein.

"Genetic alterations at this most common fragile site in the FHIT gene lead to reduced Fhit protein expression in sporadic cancers and in a much larger fraction of BRCA2-associated familial cancer," Dr. Huebner explains. "This is consistent with the idea that loss of BRCA2 function affects the stability of the FHIT site."

continued on page 15

Huebner

Structural Approaches to New Therapies: Jefferson Symposium Attracts Some of the Foremost Experts

A diverse group of scientists meeting this past spring at Jefferson demonstrated the power and the potential of structural biology and chemistry in the search for novel therapies. The symposium, "Structural Chemistry and Biology of Cancer and Immune Diseases: From Basic Research to the Clinic," was organized by Ziwei Huang, Ph.D., Director of Rational Drug Design at Jefferson's Kimmel Cancer Institute. It attracted scientists from both academia and industry and from disciplines ranging across the spectrum of basic and clinical science.

What all these scientists shared was a research approach that exploits knowledge about the molecular structure of various proteins: using these structures as templates in the design of molecules that interfere with or regulate the function of physiological systems. But these scientists' specific tactics and targets varied. Targets include cancer cells and viruses as well as the molecules involved in cell cycle regulation, immunomodulation, and angiogenesis.

Some of the new therapies developed using this structural approach have already made it to the clinic, and many more are in the pipeline.

Structural Variations Yield Different Activity Profiles

One approach with implications in the fight against both cancer and viral diseases such as HIV involves the use of molecules that are structurally similar to the nucleotides normally used as building blocks in DNA synthesis. Dr. Yung-Chi Cheng, Professor of Pharmacology at Yale University, described a new class of these agents called L-nucleoside analogs, which take advantage of the unique features of DNA synthesis in cancer cells or virally infected cells.

Currently there are several deoxynucleoside analogs, such as AZT (zidovudine) and ddC (zalatibine), which are used clinically against HIV. When these compounds get into the cells of individuals infected with HIV, they are chemically altered and then incorporated preferentially into the viral DNA, where they prevent interaction with the viral enzyme reverse transcriptase so that the DNA chain can no longer elongate, and DNA synthesis stops. While these compounds do interfere with viral reproduction without causing bone marrow suppression (an acute toxic reaction associated with other anti-viral agents), prolonged clinical use of these drugs has resulted in a delayed type of toxicity affecting various tissues and organ systems.

Dr. Cheng's lab was interested in studying the underlying mechanism of the delayed toxicity. They discovered that it was due to a depletion of mitochondrial rather than nuclear DNA, and that even slight differences in the structure of the deoxynucleosides resulted in different toxicity profiles. At the same time, his lab was searching for compounds that would be effective against the hepatitis B virus (HBV). Dr. Cheng reasoned that since HBV uses a reverse transcriptase similar to HIV, the nucleotide analogs effective against HIV might also work against HBV. Indeed, they found that anti-HIV compounds such as ddC were effective against HBV. They went on to synthesize compounds with a number of structural variations and found that different modifications yielded compounds effective against different viruses as well as compounds that interfered with the reproduction of some cancer cells.

Further, the knowledge that they are gaining about the effect of these compounds on viral infections has yielded new insight about the role of molecular structure in the phenomena of drug resistance and synergism when combinations of drugs are used.

Modulating Immunity Structurally

While Dr. Cheng searched specifically for compounds that might interfere with the virus itself, other scientists have sought means of stimulating the immune system to defend more effectively against viral diseases and cancer. Dr. Harvey Cantor, Professor of Pathology at Harvard Medical School, discussed an anti-cancer vaccine strategy that seeks to modulate the cytokines that mediate protective immune responses.

According to Dr. Cantor, the current paradigm for cytokine interaction is that interleukin-12 (IL-12), produced by macrophages and dendritic cells, imprints a Type I or cell mediated immune response. Another cytokine, IL-10, diminishes the Type I response while encouraging the humoral or allergic (Type II) response. Dr. Cantor's lab has been studying a gene called Eta-1 (for Early T-cell Activation), which is the major newly synthesized RNA in activated T-cells.

"We think that the expression of Eta-1 is an essential early link between T-cell activation on the one hand and the drive towards Type I immunity on the other; and that the engagement of its two receptors, leading to diminished IL-10 and increased IL-12, is the key to its action," he said. According to Dr. Cantor, the two effects of Eta-1 are mediated by distinct receptors that interact with different portions of the Eta-1 molecule. When one end of the molecule, the N-terminus, is phosphorylated, it engages one type of receptor and leads to IL-12 up-regulation. The other end of the molecule, the C-terminus, engages a different receptor and down-regulates IL-10.

By understanding the role that chemical structure plays in these regulatory mechanisms, Cantor hopes to be able to engineer structural modifications that will allow manipulation of this part of the immune response. "This kind of observation also opens possibilities for using this cytokine or engineered versions of these cytokines in vaccines," he said.

Interfering with Receptor Binding and Activation

Dr. Elias Lolis, Associate Professor of Pharmacology at Yale, discussed a subset of cytokines called chemokines, chemotactic cytokines that mediate inflammation. Chemokines comprise the largest family of cytokines, with over 40 distinct types identified. They play a role in immune defense, hematopoiesis, and angiogenesis.

Chemokines interact with receptors expressed on subgroups of leukocytes, white blood cells that mediate the inflammatory response.

Receptor activation initiates a cascade of biochemical reactions that regulate intracellular processes. Chemokine receptors also may bind to pathogens and this binding may be a requirement for the organism to enter the cell. The understanding of this function for chemokine receptors recently led several groups of scientists to the discovery that some individuals who appear resistant to HIV infection in fact have a mutation in the chemokine receptor dubbed CCR5. This mutation prevents the CCR5 molecule from reaching the cell surface; as a result HIV cannot bind and gain entry to the cell. Since these individuals appear to be otherwise healthy, CCR5 may be a safe target for inhibition.

Dr. Lolis has been working to define, at a structural and chemical level, the process of chemokine binding and receptor activation with the goal of designing safe and effective inhibitors. Because the chemokines are important in so many physiologic systems, compounds that modulate chemokine activity could have applications in treating a broad range of illnesses.

Structural biologists and chemists have targeted numerous other receptor/ligand binding interactions with the goal of manipulating the cell cycle. Wayne Hendrickson, Professor of Biochemistry and Molecular Biology at Columbia, discussed one of the most ubiquitous of these processes: signalling by cellular growth factors through receptor tyrosine kinases. Through different but related pathways, protein tyrosine kinases mediate the process by which a variety of growth factors and hormones exert their effects. "Many different pathways work through tyrosine kinases," Hendrickson said. "What's emerging is a nicely unified set of principles by which these actions occur."

Protein kinases transmit signals along various pathways by transferring phosphate groups to other proteins. The structural changes that result from phosphorylation may result in a gain or loss of function in that protein. One important type of protein kinases is called the cyclin-dependent kinases (CDKs).

"You can think of the CDKs as engines that drive the cell cycle, whose regulation is frequently altered in neoplasia," said Dr. Edward A. Sausville of the National Cancer Institute. Consequently, he said, "They represent a potential target for both refining prognosis and defining new therapies." In fact, the NCI is currently involved in Phase I clinical trials of a direct CDK antagonist called flavopiridol. According to Sausville, flavopiridol appears to act at two different phases of the cell cycle. In addition, different types of tumors are differentially sensitive to flavopiridol-induced apoptosis (programmed cell death), indicating that the full story of how the drug works may be more complicated than CDK antagonism—as well as more revealing about the function of the CDKs.

These are only a sampling of the approaches discussed at the Jefferson symposium, yet representative of the types of strategies structural biologists and chemists are using to understand disease processes and develop new therapies. Combined with techniques developed by Jefferson's Dr. Huang for computer design of molecules, these structural approaches promise significant advances in the battle against cancer, AIDS, and many other diseases of our time. —*Lisa J. Bain*

***FHIT**, from page 13*

An improved understanding of the FHIT gene may lead to the identification of individuals predisposed to some of the most common human cancers, and the development of new drugs that may arrest their growth.

In 1996, Dr. Huebner and Carlo M. Croce, M.D., Director of Jefferson's Kimmel Cancer Center, identified and characterized FHIT. It is located in the human genome's most fragile area, on human chromosome three in a region known as 3p14.2. The area has an exceptionally high number of DNA gaps, breaks, and rearrangements. The researchers believe that FHIT's fragility is involved in the start or progression of such cancers as esophageal, gastric, kidney, breast, and lung.

"We knew that this region on chromosome three was prone to damage by carcinogens," Dr. Huebner says, "though we don't know what those carcinogens are, or what causes the genetic breakage. In sporadic tumors, the FHIT site is damaged, and the BRCA2 gene, and maybe BRCA1, are active and can probably repair the damage.

"But when BRCA2 is missing, many cells cannot repair the damage without BRCA2's repair mechanism; and this contributes to cancer growth. Perhaps part of what BRCA2 does is to protect the integrity of the cell, especially in fragile regions. BRCA2 function appears to be important to the stability of the FHIT site.

"One of the reasons this is exciting is because of what it tells us about repair genes in general in cancer," Professor Huebner says. It is possible that FHIT and the fragile chromosome three site are also more likely to be severely damaged in tumors of people with MSH2 and MLH1, such as in colorectal cancers. Previous studies of patients from Iceland showed a loss of DNA that was significantly higher in this region in familial compared to sporadic tumors. In this study, tumors in more than 30 women with hereditary breast cancer showed variously lower amounts of Fhit. All of the women had a defective BRCA2 gene predisposing them to cancer. Dr. Huebner's researchers think that the frequency of women with a damaged FHIT in cancer cells could indicate that those with a missing BRCA2 can't repair DNA damage when it occurs in FHIT.

"Currently, we are looking at other fragile sites in BRCA2 and BRCA1 cases and in MLH1 and MSH2-associated tumors, which are deficient in DNA repair mechanisms. It would be very helpful to know which genes are affected when you lose BRCA2 repair function."

Proof that Access to New Methods of Prevention Depends on Where Patients Receive Care

How well are medical advances translated into community practice? In the case of HIV-infected pregnant women, where they get their care may make a big difference.

In 1994, researchers across the country were thrilled when they found that the anti-HIV drug AZT, taken during the second and third trimester, could reduce mother-newborn transmission of AIDS by as much as two-thirds. Along with national educational efforts, New York State mounted an information campaign, sending letters to physicians and other health care specialists, even conducting marketing campaigns to high-risk groups.

Researchers at Jefferson asked, how quickly would community practitioners (who are statistically slow to change their approaches) adopt new practices to treat poor, pregnant, HIV-infected patients? Which patients would benefit from the new knowledge?

While community physicians in New York State responded rapidly to the findings, patients in certain health care settings benefited much more than others. The researchers found that women were more likely to receive antiretroviral treatment during pregnancy if they were (1) being treated at a medical center that performed HIV clinical trials, (2) were being treated at sites paid by the state to deliver a range of specific HIV-focused services to persons enrolled on Medicaid, (3) were receiving prenatal care, or (4) were in a methadone program.

"Where women get their medical care makes a big difference in whether they get access to important advances," says Barbara J. Turner, M.D., Professor of Medicine and Director of Health Care Research at Jefferson's Center for Research in Medical Education and Health Care, who led the study. The findings were reported June 15 in the *Annals of Internal Medicine*.

The study involved the results of the Pediatric AIDS Clinical Trials Group protocol 076, arguably the biggest advance in HIV prevention yet. The trial was halted early and its results showed AIDS transmission could be substantially reduced during delivery by giving AZT to the pregnant women during the last two trimesters of pregnancy, and to the baby during the first six months of life. But because the findings were not published for nine months, Dr. Turner explains, "the news got out via news releases, educational programs for lay persons and professionals, and direct mailings to doctors" (rather than via a definitive peer reviewed journal article).

Turner

In the *Annals* paper, Dr. Turner and her colleagues examined three time periods: January 1993 until the announcement; nine months from announcement until formal journal publication; and after formal publication until September 1996. They looked at the treatment records of 2,607 HIV-infected women who delivered live children. They found that after adjusting for patient and health care delivery factors, these Medicaid enrolled women had a 21 percent increase per month in their likelihood of receiving antiretroviral therapy during pregnancy. After the formal journal publication, the rate increased more slowly.

"But we found that certain women were *more likely* to be treated," says Dr. Turner, such as those already receiving care at centers of excellence. New York State has identified centers and physicians who contract to deliver a range of HIV-related services (such as nutritional care) and to treat special medical complications. "If a woman was treated at one of these sites, she was more likely to be treated with antiretroviral therapy," Turner says.

"Similarly, if a woman was treated at a site that had earlier been part of the 076 trial, she was 50 to 70 percent more likely to receive antiretroviral therapy. That argues for care from medical centers that offer clinical trials."

Dr. Turner sees several lessons from her team's study, which was funded by the National Institute on Drug Abuse, including the possible need for a "direct marketing program after a dramatic finding such as the 067 trial. The adoption of medical advances in private practice has been statistically far slower than in academic medical centers."

Currently, Dr. Turner and her coworkers are following the data on the women through 1998 to see which groups of women received antiretroviral therapy up to two years after they gave birth.

In recognition of her expertise on health care practices, Dr. Turner has recently been appointed Medical Editor of *Hippocrates*, a journal for primary care physicians published by the Massachusetts Medical Society (publisher of the *New England Journal of Medicine*).

A Mechanism to Control Red Blood Cell and Platelet Production

Researchers at Jefferson have uncovered a potential switch that helps control the manufacture of red blood cells and blood-clotting platelets. By better understanding how the body keeps tight reins on this process, the scientists hope to someday therapeutically control blood cell production.

For our tissues to have the oxygen they crave, we need to have enough circulating red blood cells. Athletes may artificially boost the number of red blood cells (as many Olympic officials know) using a hormone, erythropoietin, which helps immature red blood cells to mature. But too many cells can cause sluggish circulation and stroke.

Controlling the amount of the hormone is one way of regulating red blood cell production. But there's another way, called "negative regulation," which involves blocking the growth and differentiation of red cell precursors. By activating the cell's own programmed suicide process, apoptosis, researchers can halt the excessive production of red blood cells.

Cesare Peschle, M.D., Professor of Microbiology and Immunology at Jefferson, Ruggero De Maria, M.D., and their coworkers at Jefferson and the Istituto Superiore di Sanita in Rome, found evidence that by activating so-called "death receptors" on the surface of immature red blood cells, an important protein called GATA-1 can be turned off. GATA-1 is crucial to the development of immature blood cells. The team reported its work September 30 in the journal *Nature*.

continued on page 18

Despite the Best Available Drugs, HIV Is Indeed Active in the Bloodstream

The best AIDS drugs are still not good enough. Scientists at Jefferson have found evidence for the first time of actively replicating HIV in the bloodstream of patients taking the most powerful anti-HIV drugs available.

Scientists knew that the combination of drugs known as HAART, highly active antiretroviral therapy, did not eradicate the AIDS virus, despite the fact that the virus could not be detected by conventional means in the patient's blood. But they thought that the drugs had at least arrested the virus from replicating. No one had been able to find active virus in the blood of patients on the drugs.

Until now. Roger J. Pomerantz, M.D., Chief of Infectious Diseases, and his coworkers examined 22 HIV-infected patients taking HAART. Using ultrasensitive molecular techniques, he and his team found evidence of active virus in the blood plasma of every patient. Their results appear November 3 in the *Journal of the American Medical Association.*

"We are the first to show that in such patients, the virus spills out of the immune cells it normally infects, and spills into the blood, possibly infecting other cells," says Pomerantz.

"We need to be able to stop replication of the virus before we think about eradication." Dr. Pomerantz also calls for better detection methods, because "in the era of HAART, we're often dealing with low levels of virus."

Pomerantz's *JAMA* article looked at people taking HAART, a combination therapy of protease and reverse transcriptase inhibitors, who had no detectable virus in their blood by the best available clinical assays. All patients had fewer than 50 copies of virus per milliliter of blood plasma. Using extremely sensitive techniques, Pomerantz's team found active virus in every person.

A recent study of patients on HAART and interleukin-2 showed that when the drugs were halted, all patients' viruses returned to earlier levels, and they developed symptoms.

Pomerantz's group also found active virus in the seminal fluid of 10 patients. They previously reported that the AIDS virus is still present in a potentially infectious, latent form in the semen of infected men taking HAART, even when no measurable virus can be found in the blood. "Now we're dealing with two things in these patients: residual HIV that's replicating, and residual HIV that's latent," he says. He's using these new findings in ongoing clinical studies to attempt to eradicate HIV in certain patients.

Drug Profiles and Tailor-made Therapies Are Needed

Researchers may be able to sidestep HIV resistance to drugs by creating drug resistance profiles of patients before they begin treatment, writes Roger J. Pomerantz, M.D. in the September 22 issue of the *Journal of the American Medical Association.* By knowing which drugs a patient is resistant to, doctors may someday custom-design therapies against HIV, and thereby improve treatment.

But certain obstacles still stand in the way, explains Dr. Pomerantz, who is Chief of Infectious Diseases at Jeff. More research is needed to understand drug resistance, and scientists must come to agreement on when a patient's viral resistance means something clinically.

In the *JAMA* editorial, Pomerantz comments on two studies published in that issue that focus on groups of patients in quite different geographic locations. Some of the patients in both studies were resistant to a commonly prescribed and frequently effective cocktail of drugs known as highly active antiretroviral therapy (HAART).

The researchers in both studies defined drug resistance differently, leading to different opinions about the degree of resistance found in the study populations.

"Two things need to be done," Pomerantz says. "We need to understand how large the problem of primary drug resistance is, and part of that means watching different geographic areas to gauge how much multidrug resistance is developing. Then, for each drug, we have to find a way to agree on what the degree of clinically relevant resistance is.

"Clinically relevant drug resistance will differ for each drug, just as it is different for penicillin and vancomycin for bacteria," he says. "We have to find out if a threefold increase in viral resistance means something about the effectiveness of one drug compared to what it means for another," he says.

In the *JAMA* editorial, he calls for medical officials to be more alert to multidrug resistance. "If you give a patient a cocktail of drugs the first time and they don't respond, and you can't find it's from noncompliance, you have to think they may have primary resistance."

Eventually, all patients may need to be profiled for both their virus's genetic makeup and their disease status, "just as we do for pneumococcus and tuberculosis before treatment," he says.

"What does it mean when you have X resistance to AZT, and at the same time, what does it mean regarding a different drug, such as a certain protease inhibitor? It would be desirable to tell patients you are this much resistant to drug X and that much resistant to drug Y, and not to these others."

Dr. Pomerantz sees the day when each anti-HIV drug will actually have a profile of standard viral resistance. "You could say to a patient, 'This is your virus, these are the drugs it's resistant to, and this is what we'll use against it.'" Tailor-made, individually designed therapies may become more common.

Dr. Pomerantz compares the current AIDS drug resistance situation to the early days of bacteriology at the turn of the century. Doctors watched how new drugs affected different patients, and devised new definitions of clinically relevant conditions. "HIV is evolving differently in different areas of the country," he says. "Defining resistance for each drug is exactly what we did earlier in the century for bacterial infections such as tuberculosis, when people were developing resistance."

Of course, detailing the precise viral genetic makeup of each HIV-infected individual would cause treatment costs to rise significantly. This would be a particular problem for Third World nations struggling against the onslaught of AIDS. Millions are infected, and many lack primary medical care. No one knows the scope of drug resistance there, Dr. Pomerantz points out, because in many cases, patients do not receive adequate medical attention, let alone consistent therapy.

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Jefferson Discovery of How to Isolate Stem Cells Could Lead to Lab Production of Blood Cells

Scientists at Jefferson have found a way to isolate hematopoietic stem cells. "This has been the elusive Holy Grail of hematology and immunology," says Cesare Peschle, M.D., Professor of Microbiology and Immunology. "Now we have found it, by identifying the first specific and functional stem cell marker."

This could lead to laboratory production of all types of blood cells, for transfusions and for innovative approaches to bone marrow transplants and gene therapy.

Dr. Peschle (who is also Chair of Hematology-oncology at Istituto Superiore di Sanita in Rome) and his coworkers at Jefferson's Kimmel Cancer Center, and in Italy, Germany, and at the University of Nevada reported their work September 3 in the journal *Science*.

Hematopoietic stem cells, created by bone marrow, have two unique abilities: to develop into any kind of blood cell and to self-renew by generating new daughter stem cells. Yet they are very rare, making up only one in 100,000 marrow cells. They have been notoriously difficult to distinguish from the blood's other progenitor cells, which are further along in the differentiation process.

"We have found a marker—KDR—which seems to be specific for the hematopoietic stem cell as compared to other primitive hematopoietic cells," Dr. Peschle says.

"The use of the stem cell is very important and broad. Having purified it, we can characterize it at a functional, phenotypic, and molecular level." Scientists can also learn to manipulate the cell in the laboratory, he says, and "to induce the stem cell to do in the laboratory what it does in the body: self-renew and differentiate to generate a huge number of red blood cells, white blood cells, and platelets." Scientists then can generate in the lab the circulating blood cells required for blood transfusions, which currently are obtained by transfusions from normal donors.

For years, researchers have had tremendous difficulty distinguishing between two types of precursor blood cells: hematopoietic progenitor and stem cells. Progenitor cells are immature cells that can differentiate into red blood cells, white blood cells, and platelets. They are used to restore patients' blood and immune systems after high dose chemotherapy or radiation for cancer. Stem cells are earlier cells which have the unique capacity to self-perpetuate. They generate progenitor cells and blood cells throughout life. Progenitors have no self-renewal capacity—they only give rise to more differentiated precursor cells.

Scientists can isolate undifferentiated progenitor cells using a marker on the cell known as CD34. This methodology was pioneered by Dr. Peschle and coworkers in a report in *Science* in 1990. But identifying hematopoietic stem cells has been more difficult, Peschle explains. Hematopoietic progenitor cells are rare: between 0.5 and one percent of bone marrow cells are progenitors carrying CD34. Yet stem cells are even less frequent, perhaps 0.1 percent of CD34 cells, or one stem cell in 100,000 marrow cells.

The problem was that there was no specific marker on the cell surface of stem cells comparable to CD34 on progenitor cells. "Once you have a marker protein for hematopoietic stem cells," Dr. Peschle explains, "you can theoretically raise antibodies against the marker, and then you can separate stem cells from other cell populations."

They focused on KDR, a protein that functions as a receptor for the vascular endothelial growth factor. KDR is expressed on endothelial cells. The scientists found that it is also expressed at low levels on CD34-positive progenitor cells. In embryonic life, primitive hematopoietic cells are made in close contact with KDR-positive endothelial cells. They argued that KDR may represent a marker for hematopoietic stem cells after birth.

They found an antibody that recognized the KDR receptor and which could isolate the KDR-expressing cells from the other progenitors in the CD34-positive progenitor population. Those cells with KDR comprised the hematopoietic stem cells but no progenitor cells.

Now Dr. Peschle and his coworkers have precisely evaluated the capability of KDR-positive stem cells to repopulate the bone marrow with blood cells after marrow transplants in animals. They can also determine the exact frequency of stem cells in the KDR-positive population.

The ability to eventually harness the hematopoietic stem cell in both the laboratory and clinic should help alleviate blood shortages for transfusions, and permit innovative approaches to marrow transplants.

Red Blood Cells, *from page 16*

The team found that turning on immature red blood cell death receptors triggers caspases, a family of 14 cysteine enzymes that degrade critical cellular proteins, such as GATA-1. This culminates in a reversible blockade of growth and differentiation of red cell precursors, which may lead to cell death. Their article in *Nature* details part of the intricate cascade of cellular events leading to activation of these enzymes in the blockade of red blood cell development.

Apoptosis is a fundamental biological process that is vital to cell differentiation and normal development. In human embryos, for example, apoptosis creates fingers from mitt-like hands. It occurs during normal aging and sometimes during irreversible cell injury from radiation and other poisons. Scientists believe apoptosis gone awry underlies neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, autoimmune diseases such as lupus, and cancer.

Apoptosis received a great deal of attention in recent years when scientists discovered that part of the reason cancer cells grow with abandon is that they lose the ability to die at a preset time.

The Jefferson group's work represents a "new frontier" in understanding apoptosis, Dr. Peschle says. He explains that "mild stimulation of death receptors and caspases induces a reversible inhibition of red cell development rather than apoptosis." This provides a key mechanism in fine tuning cell growth and differentiation.

Such a novel mechanism may be of general significance, he says, and apply to diverse cell types in addition to red blood cells and platelets. Failures in the mechanism may lead to either abnormal cell growth inhibition or excessive cell proliferation, such as occurs in some anemias and leukemias.

Glucosidase Inhibitors May Be Effective against Hepatitis

Researchers at Jefferson may have found a promising drug against the hepatitis C virus (HCV). While they are quick to point out that the drug, N-nonyl-DNJ, stopped only a surrogate virus—and not the actual HCV—from reproducing in the lab, they believe the findings, which build on their earlier success against hepatitis B virus (HBV), may someday lead to a single drug against both viruses.

HCV chronically infects some 100 million people worldwide, with as many as four million chronic carriers in the United States. Those at risk for contracting HCV include intravenous drug abusers, and anyone who had transfusions prior to 1990, when blood supply screening for HCV began. Together, HBV and HCV chronically infect more than 400 million people. Approximately one million die each year from related liver diseases, such as hepatitis, cirrhosis, and cancer.

Timothy Block, Ph.D., Professor of Biochemistry and Molecular Pharmacology at Jefferson, and colleagues at Oxford University in England used N-nonyl-DNJ to inhibit the activity of glucosidase, an important cellular enzyme. This in turn prevented the bovine diarrhea virus, BVDV, which is a tissue culture model of HCV, from making more virus. Because HCV cannot be grown in the lab, researchers use BVDV as a testing model.

Dr. Block believes glucosidase inhibitors have a reasonable likelihood of working against HCV. "N-nonyl-DNJ is the first drug since alpha-interferon to my knowledge for which there is published experimental evidence against HCV—in the form of BVDV susceptibility," says Dr. Block.

The drug may sidestep resistant viruses, the bane of current anti-hepatitis treatments. "Since the drugs target a host cellular enzyme at very nontoxic doses, rather than the virus, we think that resistance to the drugs will not be a problem," he says. The findings appeared October 12 in *Proceedings of the National Academy of Sciences*.

Viruses such as HCV, HBV, and BVDV reproduce by budding out from intracellular membranes. The viruses appear "extremely sensitive to these drugs, while the normal cellular processes are not affected," Dr. Block says. "And because we target this cell pathway, upon which a whole family of viruses is dependent, we can probably develop drugs that have broad activity" against an array of viruses.

The next steps are to experimentally test the drug against HCV and to determine why the virus is so sensitive. Potential clinical trials for the drug are still some time away.

In earlier work, and Dr. Block and his colleagues at several institutions found that N-nonyl-DNJ interfered with a specific step in the life cycle of the woodchuck hepatitis virus (an animal model for HBV), essentially shutting down its ability to infect a cell. As a result, levels of the virus in the animals' bloodstream dropped dramatically.

They found that a very specific step in the life cycle of the virus can be selectively inhibited by N-nonyl-DNJ. The drug worked by inhibiting the first step in the glycosylation process that all cell glycoproteins go through to reproduce. The virus cannot infect if it doesn't go through this step. Fortunately, the host cellular glycoproteins appear to be far less sensitive to this inhibition than is HBV, meaning that the animal's own cells are not badly hurt by the drug.

BVDV and HCV are viruses composed of RNA, as opposed to HBV, which is made up of DNA. "They have different genomes but similar methods of envelope development: budding from the endoplasmic reticulum (ER)," Dr. Block says. "We think they will all be very sensitive to N-nonyl-DNJ, since this drug blocks the first step in ER glycoprocessing which is needed for some but not all proteins to fold in the ER." In both HBV and HCV, the researchers were able to block the creation of a virus envelope, locking the virus within the infected cell. The virus thus was rendered noninfectious.

First Transgenic Mouse Model of Hepatitis B-based Disease

Jefferson faculty have developed the first mouse model of chronic liver disease caused by hepatitis B virus (HBV), which promises to accelerate the discovery of drugs against the disease.

Mark A. Feitelson, Ph.D., Professor of Pathology, Anatomy, and Cell Biology, and his colleagues have developed transgenic mice that are chronic carriers of HBV. They were made by introducing the HBV genetic information into mouse eggs, and breeding mice that had viral DNA in all of their cells. Such mice consistently replicate HBV throughout their lives. Although other similar models have been made using normal mice, none develops chronic liver disease because the immune system sees the virus as "self" during embryonic development.

To solve this problem, Dr. Feitelson used severe combined immunodeficient mice as viral hosts. These mice lack critical immune system elements that normally would fight the virus. When the mice are reconstituted with a normal immune system in a procedure akin to bone marrow transplantation, they do not recognize the virus as "self" and develop liver disease.

The researchers reported their results in August in the journal *Nature Medicine*.

"The mice see the virus as foreign, which is what they should do," Feitelson explains. This is similar to the way the human immune system recognizes HBV shortly after exposure to the virus.

In addition to chronic liver disease, these mice have also been manipulated to develop acute disease. "The differences between acute and chronic disease in these mice will be key to the development of new approaches against the latter," Feitelson says, noting that many individuals with acute disease recover.

continued on page 23

GM1 Ganglioside to Improve Parkinson's Symptoms and Delay Its Advance

Scientists at Jefferson, armed with a new $2.4 million grant from the National Institutes of Health, hope to find out whether the drug GM1 ganglioside can improve symptoms, delay disease progression, and in some cases actually restore damaged brain cells in Parkinson's disease patients. More than one million people in the United States suffer from Parkinson's.

Jay S. Schneider, Ph.D., Professor of Pathology, Cell Biology, and Anatomy, is leading a five year clinical trial involving 150 patients. It will compare the effectiveness of GM1 ganglioside—a naturally occurring substance in the nerve cell's membrane that plays a role in cell growth, development, and repair—to standard Parkinson's disease treatments, which improve symptoms but do not alter the disease process.

"We hope that we will be able to do something no one else has done before: to stimulate remaining brain cells to sprout new nerve endings and rescue other cells that might otherwise die," says Dr. Schneider, who last year published evidence in the journal *Neurology* showing that GM1 may improve symptoms and perhaps even help slow progression of Parkinson's.

"If we can stimulate repair and regrowth in humans as we've done in the laboratory, we will have evidence for the first time of a therapy that can help restore the part of the nervous system damaged by a neurodegenerative disease," Dr. Schneider says.

"Current therapies for Parkinson's disease treat only the symptoms and do little to address the underlying disease. You can alleviate some symptoms for a time, but the neurodegeneration continues."

The Jefferson team is collaborating with scientists at the University of Pennsylvania to perform a special type of imaging called single photon emission computed tomography, or SPECT. It allows the team to visualize the number of dopamine terminals in the striatum, the part of the brain that receives dopamine from the substantia nigra (the brain region that dies in Parkinson's disease). Comparing patient symptoms and the number of dopamine terminals is a significant advance, Schneider notes. "This technology will give us insight into the relationship between the expression of Parkinsonian symptoms, and the actual number of dopamine terminals in the brain."

The study is a randomized, double blind, placebo controlled trial in which neither the researchers nor the patients know who receives the drug.

Patients with mild to moderate Parkinson's disease will be divided into three groups of 50 each. One group will receive the drug during the first two study phases. Another 50 will receive a placebo during phase one, and the drug during the second trial phase. A third control group of 50 will receive neither the study medication nor a placebo, but will receive standard Parkinson's therapy. This latter group will have the option of receiving the new experimental medication after the study period ends.

"We're hoping that in the first six months of the study we'll see the same kind of symptomatic improvement we've seen in previous studies with GM1, as well as a small increase in the number of dopamine terminals," Schneider says.

Can Melatonin Help Avoid Parkinson's Damage?

Melatonin, a substance now familiar to consumers, could be a key to understanding how to treat Parkinson's disease. Scientists at Jefferson have shown in the laboratory and in test animals that melatonin is effective in preventing a type of brain cell damage similar to that found in Parkinson's.

It's widely believed that the loss of dopamine nerve cells seen in Parkinson's patients' brains, results from oxidative stress to the cells. Various cellular insults produce oxygen free-radicals, resulting in cell death. The brain's dopamine neurons are particularly vulnerable.

Melatonin, a hormone produced by the brain which is marketed commercially as an anti-aging agent, is the body's most potent antioxidant. Two years ago, Professor of Neurology Lorraine Iacovitti, Ph.D. and her coworkers showed in the laboratory that melatonin was effective in blocking the oxidative ravages of Parkinson's-damaged dopamine-producing cells. They tested the theory in rats by giving the animals a toxin, 6-hydroxydopamine, which specifically damages dopamine neurons, producing a Parkinsonian-like syndrome. They found that by injecting melatonin into the rats either 10 minutes prior to the 6-hydroxy infusion, or 30 minutes afterward, they could block the Parkinsonian effects. If they administered melatonin 120 minutes later, they were able to prevent about half the damage, or "rescue the cells."

Dr. Iacovitti presented her team's findings October 24 at the annual meeting of the Society for Neuroscience.

In oxidative stress, cells don't automatically die. Rather, they pass through a cascade of cellular events leading to cell death. Iacovitti and her team used melatonin to stop the cascade at its beginning. They plan to explore other checkpoints in the death cascade to gauge the compound's effectiveness.

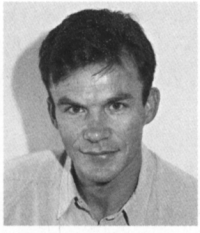
"If you get enough antioxidants to the dopamine nerve cells, you might be able to prevent the kinds of oxidative stress and cell death you see in Parkinson's," she believes. Dr. Iacovitti notes that melatonin "has the correct action to be developed pharmaceutically," but cautions that the dosages given to the test animals were extremely high. "Whether it could be developed into a safe drug is another question," she says. "It's difficult to know at what levels to keep antioxidants in the body." A drug company might be able to isolate an active part of melatonin that could be a more effective antioxidant at lower doses.

Stimulating Learning Environment May Prevent Alzheimer's

A study by a Jefferson scientist suggests that a stimulating learning environment early in life might help ward off neurodegenerative diseases later. Nurture may be more influential than nature when it comes to the brain's resilience to injury.

Researchers at Jefferson and the University of Auckland in New Zealand found that rats living in a stimulating environment filled with running wheels, tunnels, balls, and food had 45 percent less of the brain cell death commonly associated with normal development and aging, than did rats living in basic surroundings. What's more, when the stimulated rats were exposed to a neurotoxin, they suffered almost no loss of brain cells, unlike those in a normal environment. The results were reported in the April 1999 issue of *Nature Medicine*.

"We were hoping to find some scientific underpinnings to the age-old maxim 'use it or lose it,' " explains Matthew During, M.D., Director the Central Nervous System Gene Therapy Center at Jefferson.



During

Dr. During was surprised how robust the brains were in rats in a stimulating environment. "We showed in this study that an enriched environment switched on genes in the brain. By this mechanism, the brain appears to become resistant to aging, or traumatic brain injury, or diseases such as Alzheimer's and Parkinson's," he says.

"There haven't been many proper studies done in the lab to show whether actively using your brain enhances your ability to stay healthy, and what specific mechanisms might be involved in this. We asked what a stimulating environment would do to cognitive function, particularly in preventing brain cell death and brain degeneration."

The enriched learning environment for rats had running wheels, tunnels, rubber balls, a maze, and a bar-pressing food station. They could choose their food and treats, such as corn chips. Rats living in standard conditions had no toys and only one food and water source.

Other scientists have shown in recent years that brain cell growth and replacement can occur throughout development and aging in animals and humans, while brain cell death also occurs. The work by During's team provides the first compelling evidence that a stimulating environment along with early and continued learning not only protects the brain from disease, but increases its capacity to repair and regrow damaged cells. "We've shown that a learning environment can encourage cell growth, and also reduce cell death by about 45 percent (including both aged cells and young cells that spontaneously die)."

A further step in the Jefferson study was to give both sets of rats kainic acid, a neurotoxin. The brains of rats in the enriched surroundings were almost completely protected—a dramatic finding.

During and his coworkers are now unraveling the mechanism: the specific environmental components and specific interventions that are effective in protecting the brain. "We're asking whether these genes we've shown to be active are actually switched on by the environment. What specific genes and chemicals are involved? And can we use them to improve protection of the brain, and to treat neurodegenerative diseases?" Among the chemicals associated with these processes are growth factors, such as glial cell derived neurotrophic factor and brain derived neurotrophic factor, and transcription factors.

Jefferson Ranks in the Top Quarter of All Medical Schools in Training Grants

Jefferson Medical College now ranks among the top 25 percent of all medical schools in the United States in terms of training grants from the National Institutes of Health.

Of 124 medical colleges receiving NIH training grants, Jefferson is now 30th, notes Gerald Litwack, Ph.D., Associate Dean for Scientific Affairs. The ranking is based on an analysis conducted by Dr. Samuel Herman, Jefferson's liaison to the NIH in Bethesda, Maryland. "Many scientists believe that a training grant is an indicator of the significance of the research being conducted," Litwack points out.

In terms of total NIH research dollars, Jefferson is 40th nationally, or within the top third of all medical schools, Dr. Litwack adds. Amount of NIH funding is widely seen as an indicator of an institution's quality. "Jefferson is currently embarked on an organized effort to move up to the top 25 percent in total NIH dollars," he says.

"For the fiscal year ending June 1999, our research income, including NIH and all other sources, is estimated at more than $94 million. This is roughly a $10 million increase over the previous year."

Jefferson currently has about 17 NIH-supported training grants, totaling more than $2.5 million per year for training. Helping boost Jefferson into the top 25 percent in this area is a recent $1.2 million award to Jefferson's Department of Biochemistry and Molecular Pharmacology from the National Institute of Diabetes, Digestive and Kidney Diseases. The five year grant pays stipends for four postdoctoral and four predoctoral fellowships in biomolecular signal transduction. The NIH-funded faculty preceptors come equally from the Department of Biochemistry and Molecular Pharmacology and from Jefferson's Kimmel Cancer Institute.

Three of the current NIH training grants are for medical students, for summer research in cancer and blood and lung disease as well as other areas, Dr. Litwack adds. "Our success in funding medical students' summer research outpaces many notable medical schools. Every summer we generate 35 slots for first year medical students who wish to experience research." These positions are funneled through the Office of Scientific Affairs and coordinated by Professor Catherine Calkins, Ph.D.

To further increase our funding from the NIH, in order to reach our goal of the top 25 percent, Litwack says, "Our plans are to increase the size of our faculty and our research facilities."

It is likely that in the year 2002, many of the researchers and clinicians of the Kimmel Cancer Center will move into a large new building of their own on Jefferson's campus. The new structure will mean a major expansion of the total lab space on campus, enabling Jefferson to recruit many more investigators and obtain significantly more federal grant money, including training grants, than at present.

Senior Health Institute Will Guide Care to the Aging

Medical progress during the 20th century has dramatically increased life expectancy. An ever larger percentage of the population is over age 65. Many of these individuals have chronic age-related conditions such as osteoarthritis, heart disease, or dementia. Others have so far remained healthy.

Recognizing their varying needs, the Jefferson Health System has developed a Senior Health Institute to guide its efforts to improve the quality of life of older persons. The SHI draws on the expertise of numerous system members in research, teaching, and clinical practice. The objectives are:

1. To foster the development, quality, and integration of services for seniors.
The institute has created an inventory of existing JHS senior health resources, with a database accessible via the World Wide Web to increase awareness of them. Elizabeth White, M.D., a board certified geriatrician, has been appointed Medical Director of Senior Health for the system. She is organizing the medical directors of long term care facilities throughout JHS to develop quality criteria for physicians, and quality measurement processes for resident care. Dr. White is also designing wellness programs to prevent illness and disability in assisted-living and continuous care retirement communities.

2. To promote aging research within JHS.
Laura Gitlin, Ph.D., Director of Community and Homecare Research at Thomas Jefferson University's College of Health Professions, has compiled an inventory of researchers in basic science, clinical medicine, and gerontology to stimulate interdisciplinary and inter-institutional research. The computerized inventory will be accessible via the SHI Web page, to make it easy to search for investigators across the system.

Dr. Gitlin is also preparing a leadership grant application to the National Institute on Aging. The research goal is to develop methods to identify persons at high risk for disability, and provide them with services to optimize their health and prevent health-related crises. This involves appropriate screening, utilization of treatment protocols and clinical guidelines, and coordination of medical and support services efficiently across multiple health care sites.

3. To create "senior friendly" medical settings.
"Senior sensitive" hospitals and clinics will have innovative environmental and procedural refinements to improve hospital experiences for older patients. The changes will include early rehabilitation, minimization of adverse effects of medications, and formulation of thoughtful discharge plans.

4. To enhance education in geriatrics.
The directors of training programs throughout Thomas Jefferson University and the health system are developing curricula for medical students, nurses, occupational therapists, and physical therapists to cover such areas as functional assessment, theories of aging, expected physiologic changes, the continuum of long term services, and the special needs of caregivers.

Market forces have substantially and perhaps adversely affected medical practice in this country. For older adults, misaligned incentives and fragmented services have perpetuated, if not exaggerated, the preexisting deficiencies. We want to tap the ingenuity and commitment across the Jefferson Health System to protect and restore the health of older persons.

—Barry W. Rovner '80, Medical Director of the Wills Geriatric Psychiatry Program, a joint program of Jefferson and the Wills Eye Hospital

Lankenau Receives One of Five Grants Nationwide to Study the Basic Biology of Aging

Researchers led by Dr. Vincent J. Cristofalo at the Lankenau Medical Research Center, a member of the Jefferson Health System, are the recipients of a large grant from the National Institute on Aging for a Nathan Shock Center of Excellence in the Basic Biology of Aging. This is one of only five grants in the United States, the others being at Harvard University, the University of Michigan, the University of Texas at San Antonio, and the University of Washington.

The award carries funding over a four-year period to enhance support facilities for investigations and provide a stimulating environment to new researchers in the field.

Three overlapping and interrelated themes underlie the program of the Nathan Shock Center: functional changes in excitable tissues such as nerve, muscle, and heart, including dementing diseases such as Alzheimer's disease; changes in the regulation of gene expression with aging, including those changes leading to age-associated diseases such as cancer, atherosclerosis, or osteoarthritis; and mechanisms of regulation of the declining function of the immune system.

The grant currently supports five core resource units around which the research is structured. The Animal Core offers properly housed and genetically defined rodents of different ages to qualified researchers. By providing genetically defined female rats to expand studies done previously on males, this core promotes research on sex differences in life span and patterns of aging. The Cell and Tissue Core involves expanding an existing human cell bank and establishing a human tissue bank. The Brain Bank Core makes available brain tissue from human subjects with an emphasis on nonpathologic brain specimens.

Jefferson HealthCARE Opens in Voorhees

As part of its continuing effort to provide health care services to the South Jersey population, Jefferson HealthCARE-Voorhees has opened in the Voorhees Corporate Center. The new facility houses medical offices and general x-ray services. A wide array of specialties are represented, in addition to primary care.

"Now we can care for patients who are seeing Thomas Jefferson University Hospital physicians, but don't want to travel too far from home," explains Jefferson Hospital President and CEO Thomas J. Lewis. "Many of our doctors who practice in Center City already treat patients who live in South Jersey. By bringing the doctors closer to where they live, and providing a variety of specialists under one roof, we have shortened the distance between Jefferson and our patients."

Jefferson Hospital was named this year by *U.S. News and World Report* as one of "America's Best Hospitals" for cancer treatment, cardiology, gastroenterology, geriatrics, gynecology, neurology and neurosurgery, orthopaedics, otolaryngology-head and neck surgery, respiratory disorders, rheumatology, and urology.

Kimmel and Whitney Elected to Board of Trustees

The Board of Trustees of Thomas Jefferson University has elected two new members: Sidney Kimmel and Leslie W. Whitney, M.D.

Mr. Kimmel is founder and chairman of the Jones Apparel Group, a leading women's apparel manufacturer. He has long been active in supporting medical, cultural, and educational organizations nationally, with a particular focus on the Delaware Valley.

Mr. Kimmel is perhaps best known to Jeffersonians through his generous gifts to establish the Kimmel Cancer Center of Jefferson Medical College and the Kimmel Cancer Institute for research. As National Chairman of "The March," Mr. Kimmel spearheaded a program last year in Washington, D.C., that resulted in an unprecedented 16 percent increase of $400 million in federal funding for cancer research.

Mr. Kimmel has produced major films through his entertainment company and has been the lead supporter of his native Philadelphia's performing arts center, currently under construction as the new home of the Philadelphia Orchestra.

Leslie W. Whitney, M.D. has pursued a long and noteworthy career in medicine in Delaware and Philadelphia, with an emphasis on cancer treatment, education, and research. Since 1994 he has served as Director of Academic Affairs at the Medical Center of Delaware, and since 1996 as Assistant Dean at Jefferson Medical College. Since 1995 he has been Executive Director, Delaware Institute for Medical Education (DIMER) and since 1994 has chaired faculty committees on quality improvement, clinical care, and credentialing for the Medical Center of Delaware in addition to serving as Medical Director, Health Services Corporation, Medical Center of Delaware. Dr. Whitney is a Trustee of the Medical Center of Delaware Foundation. He has been principal investigator for numerous cancer research projects in Delaware through the years.

Transgenic Mouse Model, *from page 19*

The mouse model may also have implications for developing drugs to fight a major international public health dilemma. "One of the largest problems in the field of hepatitis B is what to do with carriers at high risk for the development of chronic liver diseases," Feitelson notes. "We have a vaccine to prevent the disease and tests to screen the blood supply, but there are still an estimated 350 million HBV carriers at high risk of developing hepatitis, cirrhosis, and liver cancer." As many as two billion people worldwide are infected with the virus, though they are not carriers. Chronic HBV infection is the ninth leading cause of death in the world, accounting for a million deaths annually.

While scientists know that the pathogenesis of chronic hepatitis B is due to immune responses against the virus-infected liver cells, "There are basic science questions about the pathogenesis that are unsolved and which can be addressed using our new mouse model," Feitelson says.

"We can test drugs in the liver against the virus in the absence of disease—if we don't reconstitute the immune system. Or we can replace the immune system and then ask what the drug does to the virus and the disease."

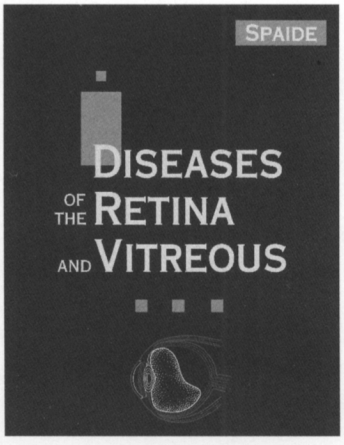
The mouse model will enable scientists to target the liver with viral gene therapy, decide which virus proteins are targets for immunological responses, and identify the parts of the immune system that are important for targeting the virus.

The model has implications for understanding other diseases as well. "Scientists can use the same approach to study the pathogenesis of immune-mediated diseases involving other infectious agents—and to study certain autoimmune diseases," he explains. "With something that is foreign, you can reconstitute the immune system and look for development of pathology to that foreign protein."

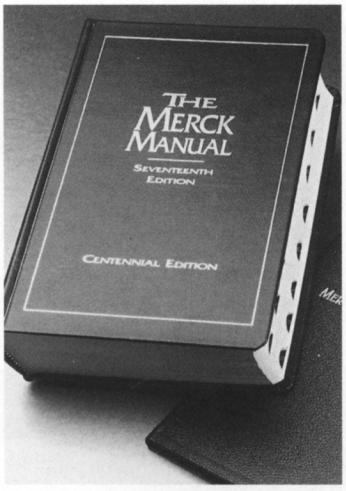
BOOKS

Arthur H. Brownstein '80 is the author of *Healing Back Pain Naturally,* published this year by Harbor Press of Gig Harbor, Washington. The book has been endorsed by Andrew Weil, M.D., a well known advocate of alternative therapies. Dr. Brownstein holds an M.P.H. in addition to his M.D. degree, and is a Clinical Instructor of Medicine at the University of Hawaii. He lives in Hanalei.

Richard Spaide '81, author of numerous papers, book chapters, and invited lectures, had a textbook, *Diseases of the Vitreous and Retina,* published by W. B. Saunders Company in August. Dr. Spaide has a large practice in New York City, and a faculty affiliation with New York Medical College. His wife Chang Ho Spaide is an '83 Ph.D. graduate of Jefferson.



Mark R. Stein '68 of Palm Beach Gardens, Florida is the Editor of *Gastroesophageal Reflux Disease and Airway Disease,* published this year by Marcel Dekker, New York as part of the series "Lung Biology in Health and Disease." Dr. Stein's volume comprises 364 pages with illustrations. Among the 13 contributors are ***Lyndon Mansfield '68*** of El Paso, Texas and ***Stephen McGeady, M.D.,*** a faculty member in pediatric allergy and clinical immunology at Jefferson and the duPont Hospital for Children.



Five Jefferson alumni contributed to the new centennial edition of *The Merck Manual.* Seventeen editions of this well known book have been published since 1899 as a nonprofit informational source by Merck and Company, the pharmaceuticals firm.

More than 10 million copies in 16 languages have been sold in this century. Rest assured, the content has changed: where the 1899 manual recommended leeches for laryngitis, this year's volume discusses resistance to antibiotics. Instead of tobacco as a treatment for asthma, there's now a chapter on smoking cessation.

The 1999 section on myoneurogenic disorders and prostate disease was contributed in part by ***Gerald Andriole '78,*** Chief of Urology at Washington University School of Medicine in St. Louis. ***Stephen Finn '92*** of Georgia wrote on gastritis and peptic ulcer disease. ***John H. Bland J'44,*** a Professor Emeritus at the University of Vermont College of Medicine, covered osteoarthritis and neurogenic arthropathy, and ***Herbert Patrick '77,*** a Jefferson faculty member and expert on pulmonary medicine, discussed sarcoidosis. ***James V. Mackell '69*** of Maple Glen, Pennsylvania was a chapter reviewer.

The "Best" Internet Sites about Health

When Jefferson neuroscientist Jay S. Schneider, Ph.D., tried to navigate the Internet in search of information to help a neighbor learn more about his daughter's rare brain tumor, he was perplexed by the difficulty of wading through vast reams of material, some of it blatantly inaccurate.

How, he asked, could the average person possibly separate the helpful, accurate information from the useless and misleading?

"A typical search may result in a list of thousands of sites containing your search word or phrase," says Dr. Schneider, a renowned Parkinson's disease expert and Professor of Neurology at Jefferson. "Out of those sites, some have erroneous medical information, and some are simply trying to sell products."

Finding no consumer guide to help, he and a colleague decided to write one.

Dr. Schneider and fellow neuroscientist Theodore I. Lidsky, Ph.D., Director of the Laboratory of Electrophysiology at the Institute for Basic Research on Developmental Disorders in Staten Island, New York, created a guide entitled *The Doctor's Always In.* Published by NeuroInformatics Publishing, it describes more than 1,100 "best" Internet sites on health and medical information.

The book's 25 chapters are broken down by body system and specific disease category, such as AIDS, allergies/asthma, cancer, gastroenterology, mental health, or sports medicine. Nearly every chapter begins with a "general information resources" section describing information on a range of topics. This is followed by descriptions of more specific sites. Each entry gives the web address and explains what the consumer can expect to find.

In the chapter on cancer, for example, the first few pages describes more general cancer information sites. The rest of the chapter focuses on specific sites, such as those for brain tumors, childhood leukemia, and breast cancer. A chapter on alternative medicine offers descriptions of sites focusing on herbal medicine, medicinal plants and foods, chiropractic, and homeopathic medicine.

The authors also include a chapter entitled "General Medical Resources," which describes sites providing material about drugs, clinical trials, and consumer information about doctors.

"In researching the book, we combed through thousands of sites for more than six months to find those that had reliable information. Many of these were from government organizations, foundations, and academic institutions," Dr. Schneider explains. Some institutions such as Jefferson (www.jeffersonhealth.org) provide both timely news and comprehensive information on a wide range of medical subjects.

"We also provide some cautionary notes about getting medical information from the Internet, which can be very different than getting it from a book or a physician.

"The book makes you a more educated consumer, allowing you to discuss your condition, medications, or side effects with your doctor," Dr. Schneider says.

The authors also include an explanation of how the Internet works, including such features as bulletin boards, listservs, and search engines.

Jefferson Art Book Now Available

A unique addition to the annals of Jefferson history, *"ADORN THE HALLS": History of the Art Collection at Thomas Jefferson University,* has been written by Julie S. Berkowitz, the University Art Historian. The 725 page book was edited by Malcolm Clendenin, Editor of the Jefferson *Alumni Bulletin.*

The richly illustrated medical/art book describes the origins and development of the Jefferson collection, comprising paintings, sculptures, architecture, decorative arts, photographs, prints, drawings, and rare medical books. Following a survey of the collection as a whole, 10 chapters trace Jefferson's chronological history in the context of its portraits and other art works which collectively delineate the spirit of the institution. The final two chapters treat nonmedical art objects (such as landscapes) and European medicine and its practitioners.

The handsome volume contains black and white photographs of 429 art works (several with closeup details), and full color photographs of 28 objects. The hard cloth cover is stamped in gold, and the dust jacket features Thomas Eakins's *The Gross Clinic.* This monumental painting is discussed in its own chapter, preceded by a chapter treating Eakins as a scientist and his relationship with Jefferson Medical College.

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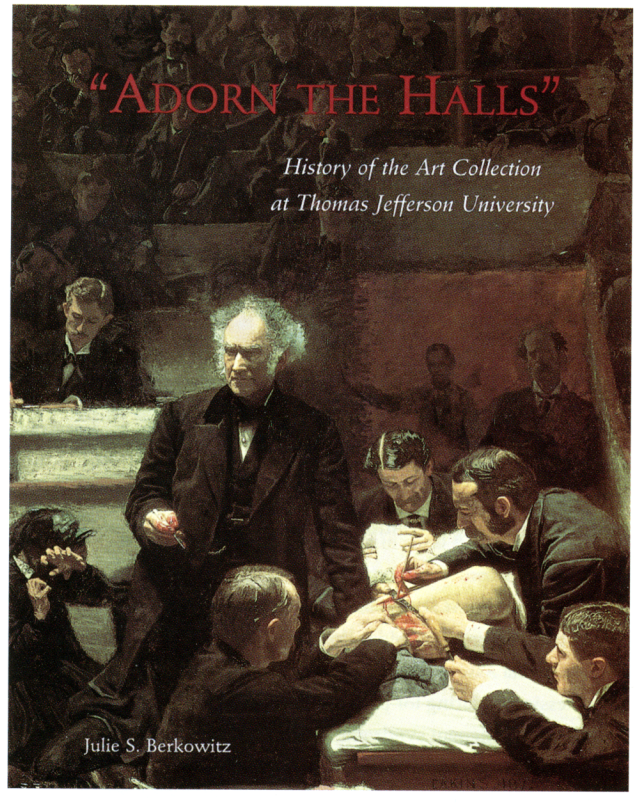

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FACULTY KUDOS

Michael A. Alexander, M.D., Clinical Professor of Rehabilitation Medicine at Jefferson and an expert on pediatric rehabilitation, takes office at the end of 1999 as President of the Medical Society of Delaware.

Alexander

Paola Luzi, Ph.D., Research Instructor in Neurology, has received an award of $30,000 from the Hunter's Hope Foundation of Orchard Park, New York. The grant supports Dr. Luzi's pilot research into gene therapy that may provide a novel delivery system for treatment of Krabbe disease.

Krabbe disease (globoid cell leukodystrophy) is a genetic disorder resulting from the deficiency of the lysosomal enzyme galactocerebrosidase. It is characterized by the progressive loss of central and peripheral myelin (a protective covering that insulates nerve cells), leading to early death. The most common form of this disease affects babies, who usually die by two years of age. Krabbe disease also affects older children and adults.

Presently, there is no cure for this condition, and treatment has been limited to cold blood and bone marrow transplantation in presymptomatic and later-onset patients. The gift from Hunter's Hope will enable Dr. Luzi and her colleagues to investigate possible gene therapy.

Hunter's Hope, founded in 1997, has raised more than $2 million to benefit research on Krabbe disease, and has also increased public awareness of this disease and other leukodystrophies (which cause degeneration of the white matter of the brain).

Michael Rhodes, M.D., Professor of Surgery at Jefferson and Chair of Surgery at Christiana Care Health System in Wilmington, Delaware, received the Curtis P. Artz Award from the American Trauma Society during the annual meeting in Washington, DC in April. The award is presented to individuals for outstanding long term contributions in the field of trauma.

Henry Rosenberg, M.D., Professor and residency director in Jefferson's Department of Anesthesiology, has been named President of the Malignant Hyperthermia Association of the United States. MHAUS provides information to professionals caring for patients with malignant hyperthermia or neuroleptic malignant syndrome. Malignant hyperthermia is a rare inherited condition characterized by a rapid, extreme, and often fatal rise in body temperature following the administration of general anesthesia. Neuroleptic malignant syndrome is a dangerous side effect occasionally seen in patients taking neuroleptic drugs for psychotic symptoms such as paranoid delusions and auditory hallucinations.

Dr. Rosenberg is Editor-in-chief of the *American Journal of Anesthesiology* and is an article reviewer for several journals. He has published extensively on malignant hyperthermia.

Lankford Receives Biomedical Engineering Grant from the Whitaker Foundation

Edward Lankford, M.D., Ph.D., Assistant Professor of Pathology, was one of 20 researchers from 19 universities who recently received Biomedical Engineering Research Grants from the Whitaker Foundation.

These grants help promising new investigators establish research careers. Dr. Lankford's award of $210,000 will support his research on the functional recovery of failing cardiomyocytes. He will explore changes that occur in human hearts after they undergo placement of implanted pumps. Such devices, which assist the failing heart by pumping blood, are inserted in individuals awaiting heart transplants, who otherwise might not survive until a heart is available.

It has been observed that patients' hearts, when supported by these devices, shrink and begin pumping more strongly, and Dr. Lankford hopes to understand the cellular changes that are responsible for this improvement. This, in turn, may enable physicians to understand why the heart function deteriorates and lead to a dramatically better alternative to heart transplantation for treating heart failure. The research requires the design, construction, and use of a new device to study very small samples of human heart tissue, especially the tissue's ability to contract and perform work.

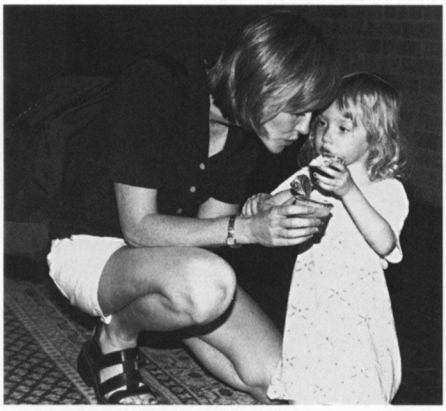
"Since heart failure is the most common reason for hospitalization today and there is an insufficient number of hearts available for transplantation, most patients will not receive transplants," Dr. Lankford noted. "Therefore, we need to be able to coax the failing heart into sustaining the patient's life and some level of activity for as long as possible. This research should help us understand how the heart muscle cells adapt to the load imposed on them, and allow us to design dramatically new therapy for heart failure. We are very excited about the potential of this research that we will be able to conduct with the three-year Whitaker Foundation grant."

The Whitaker Foundation of Rosslyn, Virginia is a private, nonprofit foundation dedicated to improving human health through the support of biomedical engineering. It was established in 1975 upon the death of U. A. Whitaker, founder and Chief Executive Officer of AMP Incorporated, now the world's largest manufacturer of electrical connectors and connecting devices. The foundation has awarded more than $450 million to colleges and universities for faculty research, graduate fellowships, and program development in biomedical engineering.

Another recipient of a Whitaker Foundation grant is Jefferson alumnus Mark Brezinski M.D./Ph.D.'88, who currently teaches at Harvard Medical School and Massachusetts General Hospital.

The Class of 2003

Jefferson students are a very select group: the 223 members of the Class of '03 were chosen from a total of 8,171 who applied for admission. Members of this class hail from 22 different states as well as Canada, and attended 91 different colleges. Forty-six percent of the class is female. No fewer than 34 students already hold master's degrees; two have Ph.D.s. Ages range from a very young 19 up to a wise 44. The age range reflects the fact that many have already achieved distinction in other careers.



Krissa George balances the books with motherhood: on the first day of the semester, bookbag over her shoulder, she tends to young Annalise. Before coming to Jefferson, Krissa was a health administrator for an international finance firm, as well as a mother of two.

Health care is familiar to many of them: there are a handful of nurses, a clinical epidemiologist, a researcher in an academic program in bone marrow transplant, an infants' nutrition counselor, a pharmacist, a pediatric audiologist, a researcher in a hospital department of maternal-fetal medicine. One has been a professional counselor for victims of sexual assault or domestic violence.

One new student spent two years as a Peace Corps volunteer in Guinea, West Africa, teaching calculus in French to high school students. Another volunteered in Croatia, working with refugee children. A third volunteered in Mother Theresa's hospital in Calcutta, India.

We know that Jefferson students can perform: there are a concert cellist, a classical guitarist, a professional clown, and a TV comedy writer. But management skills are not lacking: one freshman was a director of international sales for a computer game company. And technical skill is taken for granted: there are several engineers, including one specializing in submarines.

The Class of 2003 was selected under the leadership of Benjamin Bacharach '56, who served until recently as Associate Dean for Admissions, and is now Associate Dean for Alumni Relations and Acting Executive Director of the Alumni Office. The selection of next year's entering class is now being overseen by Clara A. Callahan PD'82 as Associate Dean for Admissions and Student Affairs.

At right: Associate Director of Admissions Grace Hershman and Assistant Dean for Student Affairs Karen Glaser, Ph.D. with first year student Denise Markmann (second from right) and her parents Margaret and William Markmann ORS'79

JAMA Study Proves That PSAP Brings Family Physicians to Underserved Areas

Despite an oversupply of physicians in the United States, statistics show that rural areas continue to suffer from a shortage of physicians, especially family doctors. In response to this maldistribution, Jefferson Medical College initiated the Physician Shortage Area Program (PSAP) in 1974 to increase the number in underserved regions, especially in Pennsylvania.

Now 25 years old, the PSAP, which admits approximately 15 students per year, graduates 12 percent of all rural family doctors in Pennsylvania. A retrospective study demonstrating PSAP's effectiveness in easing the shortage of rural physicians appeared in the January 20, 1999 issue of the *Journal of the American Medical Association*.

The program recruits students who have grown up in a rural setting and who are committed to practicing family medicine in a similar area. "The selection process of students for the PSAP has been key to the successful retention rates," explains Howard K. Rabinowitz, M.D., Professor of Family Medicine at Jefferson and director of the PSAP since 1976.

PSAP students follow a curriculum similar to their non-PSAP classmates, but receive training in small towns and are guided by an academic advisor from Jefferson's Family Medicine Department.

The *JAMA* study used current data on 206 PSAP graduates from the classes of '78 to '91 who are presently practicing family medicine in underserved areas of Pennsylvania. They were compared against all allopathic (M.D.) medical school graduates in the state, and against all U.S. and international graduates. The PSAP graduates were also compared against their non-PSAP peers from Jefferson Medical College regarding their U.S. practice location, medical specialty, and retention for the past decade.

Results show that PSAP graduates, who represent only one percent of the graduates of Pennsylvania's seven allopathic medical schools, account for 21 percent of family physicians practicing in rural Pennsylvania coming from those medical schools. Among all national and international medical school graduates, PSAP

continued

Med. Media Services

alumni represent 12 percent of all family physicians in rural Pennsylvania. Results were similar for PSAP graduates practicing in other underserved regions.

Overall, PSAP alumni were eight times more likely than their non-PSAP classmates at Jefferson to practice family medicine in a rural area of the U.S. Program retention was also found to be high, with the number of PSAP graduates practicing in underserved areas being approximately 90 percent of the number practicing 10 years ago.

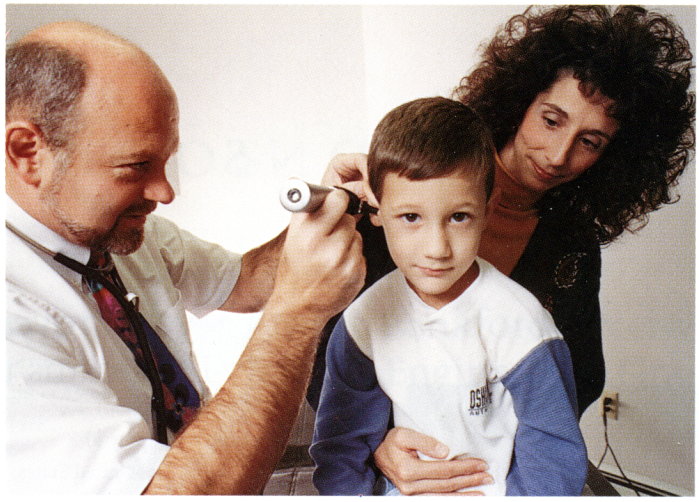
Rural family practice truly means care for the family as a whole. Physicians treat each generation, providing general medical attention plus such specialty services as delivering babies and minor outpatient surgery.

"With more rural residents in Pennsylvania than in any other state in the nation, the medical needs of this population are great, and Jefferson's PSAP is meeting these needs to a large extent," Dr. Rabinowitz says.

For ***James Devlin '85,*** medical training began as a child when he accompanied his father, a family physician, on house calls in Brockway, a small rural community in western Pennsylvania. A graduate of the Physician Shortage Area Program at Jefferson, Devlin today practices family medicine in the same town, bringing his two children with him on house calls, much the way his father did a generation ago.

"Growing up in Brockway, I watched my father get to know his patients as people, by really sharing in their lives," says Dr. Devlin. "I knew that I wanted to return to this atmosphere and practice medicine in much the same way. The PSAP gave me the training I needed to care for people."

Through the PSAP, Dr. Devlin was able to take his clinical rotations during his junior and senior years of medical school in rural parts of Pennsylvania. This exposed him to both inpatient and outpatient settings, giving him hands-on understanding of how to work in a relatively isolated area.



A visit to Dr. Devlin is not too scary.

It'll be as good as new in no time, Dr. Devlin assures.

"It means providing a wide range of care for the entire family," Devlin explains. In Brockway, he practices primary care in the sense most city dwellers know it, but also delivers babies and assists with various surgeries such as gallbladder removal, hysterectomy, and caesarean sections. Dr. Devlin treats grandparents for the general health problems of old age, while delivering their great-grandchildren. "There is a limited number of subspecialists here, broadening the scope of what I am called upon to provide."

"The PSAP's goal was to return me to the place I had loved since childhood. I am able to care for patients who are also my friends. This is family medicine in its purest form. Interestingly, it's also very modern: in the past decade there's been more and more emphasis nationwide on primary care."

A '93 graduate of Jefferson's Physician Shortage Area Program, ***Thane Turner*** of Lock Haven, Pennsylvania has experienced the program's benefits both as a student and as a teacher.

Enjoying the history and people of Lock Haven, Dr. Turner knew that he wanted to return there to practice medicine, caring for the friends and family he had known for a lifetime. "Practicing in the country allows me to learn not only my patients' medical histories, but also their family histories and life experiences," he says.

"The PSAP allowed me to complete training during my clinical years of medical school in rural areas, and also to conduct some interesting academic research," he says. "I was able to build relationships with my mentors on the Jefferson faculty, who showed me the scope of what you can do in family medicine."

Turner put his training to work in a group medical practice in Lock Haven,

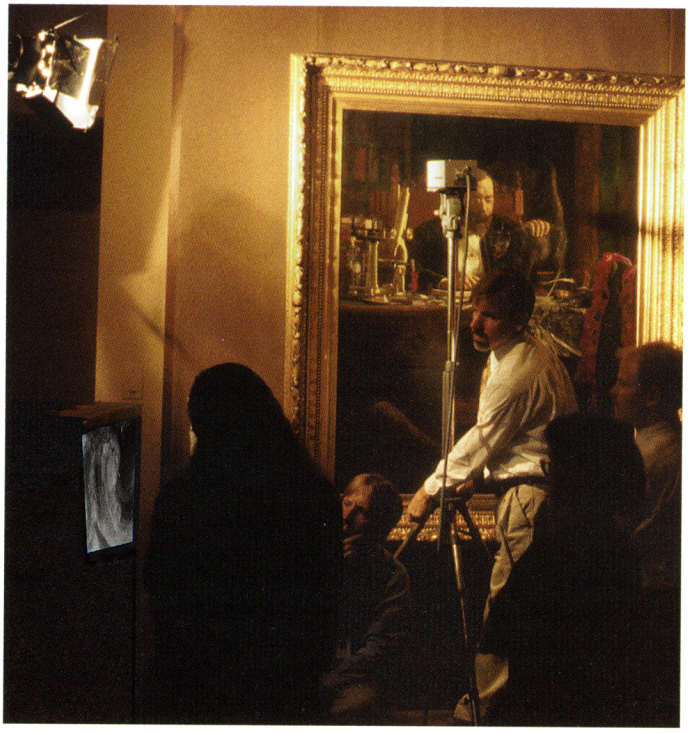
Stuffed animals lend support on the right as the boss consults Dr. Turner.

where he lives with his wife and two children. He provides comprehensive care—everything from treating patients for the flu to delivering babies, performing minor surgeries (such as suturing or mole removal), and casting minor fractures.

Like all PSAP participants, Dr. Turner studied under a physician preceptor for six weeks in a rural part of Pennsylvania in his fourth year of medical school. He found the experience so beneficial that he has since served as a preceptor for current Jefferson students.

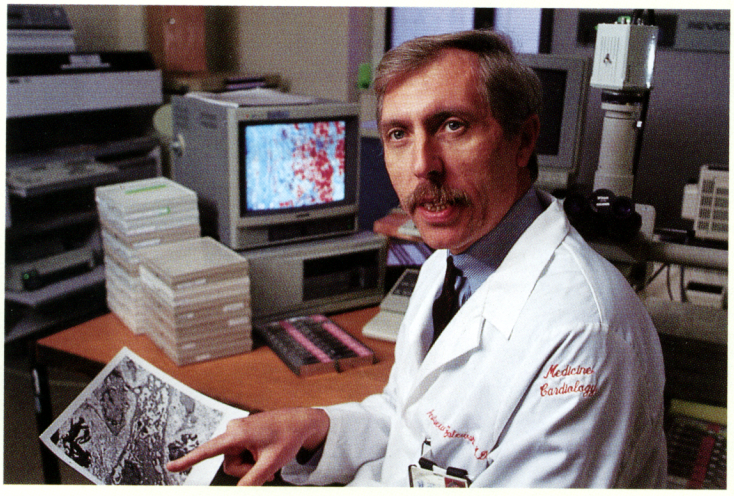
"Being a preceptor has allowed me to experience the benefits of the PSAP from the other side," Turner says. "I was able to keep my teaching skills sharp, and to bond with my student in much the same way as I had with my advisor. The PSAP allows both students and teachers to learn the dramatic differences between the practice of medicine in Center City Philadelphia and rural Pennsylvania."

Technology Illuminates a Work of Art



Joe Mikuliak

The university's Portrait of Professor Benjamin H. Rand, *a major early painting by Thomas Eakins, was studied over the summer by experts from the Philadelphia Museum of Art using infrared reflectography. Above, Mark Tucker, chief painting conservator at the museum, aims a camera which produces a greatly magnified view on the monitor at left. Infrared light has the ability to penetrate layers of paint, revealing preliminary underdrawings and compositional grids that Eakins made on the canvas. This provides a new understanding of his working methods as an artist. The three Eakins portraits at Jefferson were among many of the artist's works studied by the team. Looking on during the process are curators, conservators, and photographers from the museum. Coordinating Jefferson's participation in the study was Julie S. Berkowitz, University Art Historian.*



Zalewski Appointed to William Wikoff Smith Professorship in Cardiac Research

Andrew Zalewski CD'84, Professor of Medicine, has been appointed to the William Wikoff Smith Chair in Cardiac Research. Dr. Zalewski, who is the Director of Jefferson's Cardiovascular Research Center in the Division of Cardiology, is a leader in the field of vascular biology and interventional cardiology. He and his group have published extensively on the mechanisms of vascular repair under physiological and disease-related conditions. Under Dr. Zalewski's direction, Jefferson's Cardiovascular Research Center has become a nationally recognized program bridging basic sciences with clinically relevant issues of coronary restenosis, bypass graft disease, and atherosclerosis.

A native of Warsaw, Poland, Dr. Zalewski received his M.D. degree from Warsaw Medical School, where he did his internship and residency. He has been associated with Jefferson since 1983, when he initially served as a Fellow in Cardiology. He is a member of the American Heart Association, the American Physiological Society, and the North American Vascular Biology Organization.

The William Wikoff Smith Chair was established by the W. W. Smith Charitable Trust of Newtown Square, Pennsylvania. During this past year, the trust completed its commitment to endow the chair. "This grant was given as a reflection of Mr. Smith's exceptional vision and his desire to enhance medical excellence," said Mrs. Mary L. Smith, his widow and trustee of the Smith Trust. "It is an honor to be a partner with Jefferson and its professionals who are at the forefront of heart research." —Roslyn Levine

Robert Neroni

Dr. Zalewski; Ms. Deborah J. McKenna, who is a member of the trust's staff and a daughter of Mrs. Smith; Mrs. Mary L. Smith; Mrs. Louise A. Havens, grant administrator of the trust and a daughter of Mrs. Smith; and University President Paul C. Brucker, M.D.

President's Club Dinner Celebrates Successful Completion of the Jefferson 2000

Mrs. Samuel M. V. Hamilton, longtime university trustee and Chairman of the Jefferson 2000 Fund capital campaign, was the honored guest at this year's President's Club dinner. The annual dinner dance, hosted by President Paul C. Brucker, M.D. and his wife Joan, was a glittering celebration of Jefferson's 175th anniversary and the extraordinary philanthropy that recently brought the comprehensive fund-raising effort to a close, ahead of schedule and ahead of its $200 million goal.

The event, which acknowledges Jefferson's most generous and loyal benefactors, was held Saturday evening, October 2, at the Crystal Tea Room. The evening's program paid tribute to Mrs. Hamilton for her exceptional philanthropic leadership at Jefferson, and recognized 22 new President's Club Fellows and 13 new members of the Winged Ox Society.

"One hundred and seventy-five years ago, our founders had a mission, and I am proud to say it has been fulfilled," Dr. Brucker said. "This is a very different world than it was in 1824. Both eras have their unique challenges, but I think our founders would be pleased to see how Jefferson has flourished."

"We did it!" Mrs. Hamilton told the group. "The Jefferson 2000 Fund has reached its goal—in fact exceeded it. The grand total is $202 million in gifts and pledges."

Jack Farber, Chairman of the Board of Trustees of Thomas Jefferson University, made a special presentation to Mrs. Hamilton. "We have you to thank, Dodo, for leading this campaign to victory," he said. "The more than $200 million you have inspired all of us to raise will benefit countless patients now and in the future, educate generations of physicians and other health care professionals, and advance vital research."

Mr. Farber unveiled a photographic portrait of Mrs. Hamilton as a gift to her and her family. An identical one will be displayed at Jefferson, to be replaced later by an oil portrait of Mrs. Hamilton.

"Dodo's steadfast support has had a major impact on this institution," Mr. Farber said. In addition to leading the successful Jefferson 2000 Fund campaign, Mrs. Hamilton has been a member of the Board of Trustees for 27 years, and a member of the hospital's Women's Board for more than 40 years.

During the program, Mrs. Hamilton acknowledged special donors. "For over two decades, new Fellows of the President's Club have received gold-headed physicians' canes, symbolizing healing, and acknowledging their exceptional generosity," she said. In announcing the names of the new Fellows, benefactors

d Campaign

whose total support has been $50,000 or more, Mrs. Hamilton reported that there were a record number of canes to present.

The 22 new Fellows of the President's Club include: postgraduate alumnus Thomas Connelly D'85; Mrs. Catherine Datz; Michael D. Ellis '70; Mr. and Mrs. John Estey; Martin Feldman '62; Mr. and Mrs. Stanford Frank; Mr. and Mrs. Robert French Jr.; Joshua Gold; George Hollander '39; Mr. and Mrs. Harold Honickman; W. Bosley Manges S'44; Alice T. Muffly; John J. Murray; Mr. and Mrs. Daniel Polett; Dr. and Mrs. Robert Poole III '53; Robert A. Shopbach, M.D.; Grafton F. Sieber '57; and Paul E. Stroup '52.

Richard L. Steelman Ph.D.'77 attended the dinner and received his gold pin signifying membership in the Winged Ox Society, which honors benefactors who have contributed $10,000 or more to Jefferson in the previous fiscal year. New members this year are: Mrs. William M. Cashman; Dr. and Mrs. Eui K. Chung; Dr. and Mrs. Won S. Cynn; Edward A. Emmett, M.D.; Mr. and Mrs. Stephen Klein; Karl G. Klinges '56; Mr. and Mrs. Leonard Korman; Mr. Howard S. Kroop; Helyn L. Romberg; Mr. and Mrs. Frank Schreiner; Frederick A. Simeone, M.D.; and Mrs. Henry Stofman.

Bottom row, from left: *Dr. and Mrs. Robert Capizzi and Mrs. Hamilton; Mrs. Hamilton is congratulated on her portrait by Mr. and Mrs. Farber and Dr. and Mrs. Brucker; Mrs. Benjamin Bacharach with Dr. Bacharach '56, Associate Dean for Alumni Relations and Acting Executive Director of the Alumni Association; Mrs. James Kelly '39 with Dr. Brucker.*
Middle row: *Dr. and Mrs. Stanton Smullens '61; James Stratton and Mr. Farber; Julian Feldman '58 with William Keane, M.D. and Ronald Bolognese, M.D.; Eric Hume ORS'83 with Dr. Brucker and Jerome Cotler '52 and Mrs. Hume.*
Top row: *Dr. and Mrs. Poole; Mr. and Mrs. Michael Murray and Mr. and Mrs. James Datz; Mrs. James Corwin '56 with George Gowen '52 and Dr. Corwin; (between rows) Dr. Brucker and Mrs. Muffly; (at top) Dr. and Mrs. J. Wallace Davis '42 and Mrs. Stofman; (between rows) Marianne Ritchie '80 with Dr. and Mrs. Everett Gordon '37 and Stuart Gordon '81; Mr. and Mrs. Honickman.*

photos Robert Neroni—montage Med. Media Services

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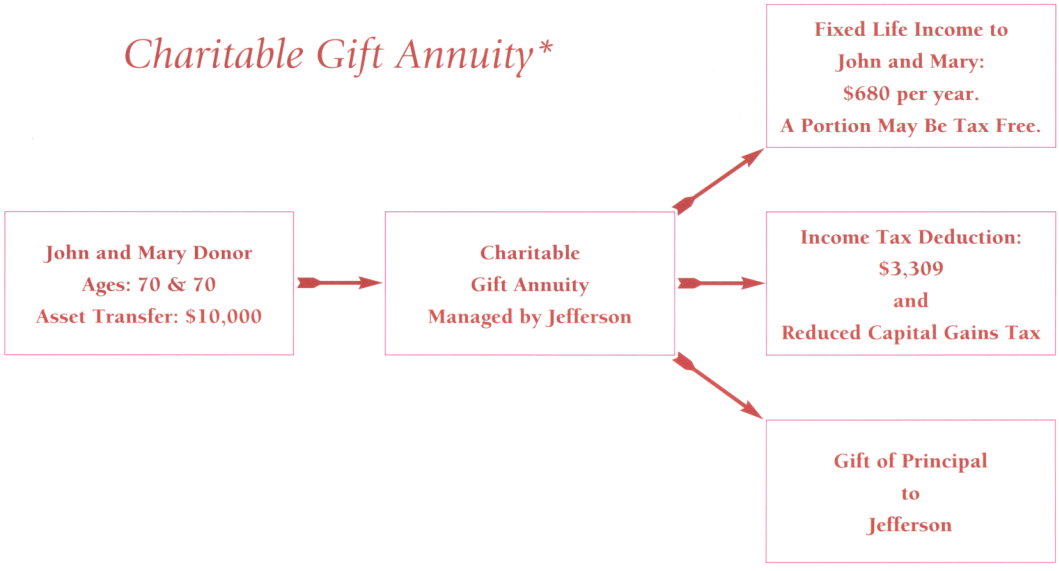

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Maus, Flanagan, and Rosenwasser

Neurosurgery and Ophthalmology Collaborate on Sophisticated Operation

In a combined operation that brought together state-of-the-art ophthalmology and neurosurgery, physicians at Will Eye Hospital removed a benign but recurring tumor from the optic nerve of patient Dolores Breskie. The five-hour operation had a sight-saving, as well as a life-saving, outcome for Ms. Breskie, who had already lost vision in one eye.

"It was the third time the tumor had grown back," says Joseph Flanagan '63, Professor of Ophthalmology at Jefferson Medical College and the attending surgeon who had removed the earlier growths. "It wasn't malignant, but it was behaving the way a malignant tumor does—aggressively," says Marlon Maus '85, an associate surgeon on the Wills oculoplastic service. "It had spread quickly, covering her optic nerve, her sinuses, and several muscles. It had also grown very large."

So large, in fact, that by the time of the operation, the tumor was the same size as Ms. Breskie's eye, and it was pushing against it, causing it to bulge unnaturally. "Her appearance just added to her distress," says Dr. Flanagan.

But it was the direction the tumor was taking that especially concerned the physicians. "It was growing dangerously close to the area of the brain where the optic nerve centers the orbit," Flanagan explains, "so it was likely to spread into the brain." It was also likely to cost her the vision in her good eye.

Under these circumstances, the surgical approach changed, evolving into a procedure requiring both an ophthalmic surgeon and a neurosurgeon. Furthermore, unlike many of the ophthalmic/neurosurgical procedures done at Wills, it was going to be open-skull surgery.

"We do a lot of ophthalmic tumor surgeries jointly, but most are only in the orbit so they can be removed without disturbing the brain," says Robert Rosenwasser, M.D., Chief of the Division of Cerebrovascular Surgery and Interventional Neuroradiology at Jefferson and Wills. "But this one was very deep and very far back, almost resting on the optic nerve. That fact moved it into the category of brain surgery."

Dr. Rosenwasser conducted the first part of the surgery, removing a portion of the skull and orbit, and slightly shifting the brain to enable the ophthalmic surgeons to reach the growth.

"We were looking down at the eye," says Daniel Elizondo, M.D., an oculoplastic fellow who assisted in the surgery, "and could clearly see the tumor and all of the tissue it had covered."

The next phase was Dr. Flanagan's, who, assisted by Dr. Maus, spent three hours removing the tumor. "It's a procedure that takes a lot of time because we try to get all of the tumor, or as much as possible," Flanagan explains.

Once it had been removed, steps were taken by Dr. Rosenwasser to decrease the chance of its return and to preserve the eye. This required removing areas of the muscles and nerves which had been invaded. "Although she has no vision in the affected eye, it was very important to her not to lose her eye," Rosenwasser says.

After the cranial closure by Dr. Rosenwasser, Drs. Flanagan and Maus rebuilt the bony area from the patient's forehead to the cheek that had been destroyed by the tumor.

"We saw her four hours later and she was wide awake, alert, and feeling very well," Flanagan recalls. "I'm grateful they were able to save my eye," declared Ms. Breskie shortly afterward.

An Albanian boy watches the convoy of American army vehicles pass by (photo by Ben Starnes '92).

Caring for the Ill and the Wounded in Kosovo

Among the Jeffersonians who contributed to humanitarian efforts in the Balkans this past spring is Benjamin Starnes '92. Starnes is senior surgeon of the 212th Mobile Army Surgical Hospital—the only remaining MASH in the U.S. Army—which was deployed to Tirana, Albania with Task Force Hawk in April 1999. They were the medical support for the proposed deep strike of Apache helicopters into Kosovo. In Albania they saw more than 700 patients and did 28 operative cases. Providing care was complicated by the sheer numbers of refugees.

Starnes also journeyed to Camp Bondsteel in Kosovo. The MASH then moved to Macedonia to back up Task Force Falcon and the implementation of Kosovo Force, the NATO peacekeeping force. "The initials KFOR are painted on everything that has any connection with it," Starnes says.

This fall Starnes was re-stationed in Heidelberg, Germany where he leads a general surgery service. His team is scheduled to return to Kosovo in March 2000 for six months as part of continued peacekeeping efforts. It's a matter of helping wounds to heal.

Starnes (right) performing a diagnostic peritoneal lavage in the trauma resuscitation bay in Albania last spring

Starnes (right) and a fellow surgeon in front of the MASH in Tirana

IN MEMORIAM

Howard E. Dieker '29 died February 6, 1999. A member of the Alpha Omega Alpha Honor Medical Society, he was in general practice in South River, NJ from 1931 to 1970. He is survived by his wife, Alice.

Charles Duffy Sr. '30 died April 10, 1999. He was in general practice in New Bern, NC. He is survived by two sons and a daughter.

Samuel J. Bishko '31 died July 12, 1999. He was in general practice in Cleveland, OH. He is survived by a son and a daughter.

Lucian J. Fronduti '34 died August 27, 1999. Board certified in general surgery and a Fellow of the American College of Surgeons, he was Chief of the Surgical Service, Citizens General Hospital, New Kensington, PA. He is survived by his wife, Jean Rita, and two sons. Son Robert is Jefferson '66 and son Ronald is Jefferson '77.

James N. Barroway '35 died September 19, 1999. Board certified in pediatrics and a Fellow of the American Academy of Pediatrics, he was on staff at Cooper and Our Lady of Lourdes Hospitals, Camden, NJ. Later he served as the Health Coordinator for the Camden County Division for Children. He is survived by a son and a daughter. Son Robert is Jefferson '64.

Charles W. Hoffman '35 died June 29, 1999. He practiced obstetrics and gynecology in South Amboy, NJ. He was Chief of Staff and Chief of Obstetrics-Gynecology at South Amboy Memorial Hospital. He is survived by four daughters and a son.

Louis A. Wikler '37 died August 23, 1999. Although board certified in pediatrics, he practiced as a family physician in Abington, PA. He was on staff at Abington Memorial Hospital, Abington, PA and the Albert Einstein Medical Center, Philadelphia, and served as the Police Surgeon for Abington Township for 25 years. He is survived by three daughters.

Warren S. Shepherd '38 died July 14, 1999. Board certified in family medicine, he practiced in Vancouver, WA. A Fellow of the American Academy of Family Practice, he was on staff at St. Joseph and Vancouver Memorial Hospitals, Vancouver, WA. He served as President, Clark County Medical Society in 1948. He is survived by his wife, Frances, two sons and two daughters.

James L. Gardner '41 died June 1, 1999. Board certified in general surgery, he practiced in Ellwood City, PA. A Fellow of the American College of Surgeons and a founding member of the American College of Abdominal Surgeons, he was on staff at Ellwood City Hospital, Ellwood City, PA, and Jameson Memorial and St. Francis Hospitals, New Castle, PA. He is survived by two daughters and four sons. Son James L. II is Jefferson '72 and son Stuart is Jefferson '79.

Joseph J. Rupp '42 died October 2, 1999. He was board certified in internal medicine and became a widely recognized endocrinologist. A revered teacher at Jefferson, he received the Lindback Teaching Award in 1964, was selected by graduating Jefferson students to administer the Hippocratic Oath in 1967 and again in 1971, and had his portrait presented to Jefferson by the Class of '69. He was a prolific writer in the field of endocrinology. A Fellow of the American College of Physicians and a member of the Endocrine Society and the Society for Experimental Biology and Medicine, he became Professor Emeritus of Medicine on his retirement in 1981. He is survived by his wife, Romaine, three sons and two daughters. Son James is Jefferson '80 and son Michael is Jefferson '84.

John J. Hosay '43 died April 10, 1999. Board certified in urology and a Fellow of the American College of Surgeons, he was Chief of Urology at the Jersey City Medical Center and St. Francis Hospitals, Jersey City, NJ and served as President of the Staff at St. Francis Hospital. He held a faculty appointment as Associate Professor of Urology at the New Jersey College of Medicine and Dentistry, Newark, NJ. He received the St. Francis Hospital Medal of Honor in 1987 and was selected "Urologist of the Year" by the National Kidney Foundation in 1992. He is survived by his wife, Lois, four daughters and two sons.

Thomas E. Pilla S'44 died July 4, 1999. Board certified in internal medicine, he practiced in Huntingdon Valley, PA. He was on staff at Abington Memorial Hospital, Abington, PA. He is survived by his physician wife, Kathleen Scott, three daughters and a son. Son Timothy is Jefferson '82.

Henry G. Gallagher '46 died March 27, 1999. He was a family practitioner in Dallas, PA. We have no further information at press time.

John J. Meehan '47 died August 29, 1999. Board certified in internal medicine, he was an attending cardiologist at Holy Redeemer Hospital, Meadowbrook, PA. He is survived by his wife, Dorothy, four sons and a daughter.

Harold Rovner '49 died August 21, 1999. Board certified in colorectal surgery, he was a Clinical Assistant Professor at Jefferson. He was also on staff at Methodist Hospital in Philadelphia. He was a former President of the Pennsylvania Society of Colon and Rectal Surgeons. He is survived by his wife, Bertha, two daughters and a son.

Juan E. Veve '49 died August 29, 1999. He was in general practice in Fajardo, PR where he was highly regarded for his compassionate care and for his charity work among his patients. He was on staff at the Fajardo District Hospital and was a member of the Puerto Rico Medical Association. He is survived by his wife, Teresa, two sons and a daughter.

Carl G. Pierce Jr. '50 died July 26, 1999. Board certified in family medicine, he practiced in Rehoboth Beach and Lewes, DE. He was a Fellow of the American Academy of Family Practice. He is survived by his wife, Meredith, three daughters and two sons.

Michael B. Dooley '52 died September 2, 1999. Board certified in radiology and a Fellow of the American College of Radiology, he was Chief of Radiology, Phoenixville Hospital, Phoenixville, PA where he also served as President of the Medical Staff in 1971. He held a faculty appointment as Clinical Assistant Professor of Radiology at Temple University School of Medicine. He was a former President of the Pennsylvania College of Nuclear Medicine, the Pennsylvania Radiologic Society, the Philadelphia Roentgen Ray Society, and the Chester County Medical Society. He is survived by his wife, Bettie, four sons and four daughters.

William F. X. Coffey Sr. '53 died September 23, 1999. An internist, he was on staff at Fitzgerald Mercy Hospital, Darby, PA. Interested in life insurance medicine, he served as Medical Director, Metropolitan Life. He also served as Chairman, Insurance Medicine Section of the College of Physicians of Philadelphia. He is survived by his wife, Roseanita, five sons and four daughters.

John W. Stoker '55 died February 20, 1999. Board certified in obstetrics and gynecology, he practiced gynecologic oncology in Altoona, PA. He was Chief of Obstetrics-gynecology at Altoona Hospital, and a consulting physician, Roaring Springs Hospital, Roaring Springs, PA. He served as President of the Blair County Medical Society in 1971-72. He is survived by his wife, Elaine, a daughter and a son.

Maurice J. Ward Jr. '63 died September 14, 1999. He was a radiologist and practiced at the Brandywine Hospital and Trauma Center, Coatesville, PA. He is survived by his wife, Marie, two sons and two daughters. Daughter Kristine is Jefferson '91.

Stanley J. Yoder '64 died June 14, 1999. Board certified in orthopaedic surgery and a fellow of the American Academy of Orthopaedic Surgeons, he practiced in State College, PA. We have no further information at press time.

Stanton M. Raynes '69 died May 5, 1999. Board certified in pediatrics, he practiced in Bensalem, PA. He was a senior attending at Frankford Hospital, Philadelphia, PA. He is survived by his wife, Maxine, and four sons.

Postgraduate Alumni

Hasib Tanyol GE'54 died June 17, 1999. He practiced in Fort Washington, PA and was on staff at Germantown Hospital, Philadelphia, PA and Montgomery Hospital, Norristown, PA. His research on hypertension and hepatic cirrhosis was published. He is survived by his wife, Lamia, and three daughters.

Benny G. Quinones-Alamo AN'82 died June 29, 1992, it has been ascertained. Other than he practiced in Rio Predras, Puerto Rico; we have no further information at press time.

Faculty

Hyman Menduke, Ph.D., Honorary Professor of Biochemistry and Molecular Pharmacology, died September 23, 1999. He was an expert in statistics and, for 35 years, taught statistics at Jefferson and assisted with the analysis of medical and research data for clinicians and medical scientists. He is survived by his wife, Clara, a daughter, a stepson and a stepdaughter.

William C. Stainback, M.D., Honorary Professor of Surgery, died August 19, 1999. He served as Chief of Surgery, Bryn Mawr Hospital, Bryn Mawr, PA and was a supportive and contributing teacher in Jefferson's surgical resident education program. He is survived by his wife, Sallie, two daughters and two sons.

Margaret "Linda" Gonnella died September 16, 1999. She was the wife of Joseph S. Gonnella, M.D., Jefferson's Senior Vice President for Academic Affairs and Dean of Jefferson Medical College. A graduate of the University of Oregon, Mrs. Gonnella moved to Wallingford 30 years ago to raise her family. She received the Wallingford/Swarthmore school district All Service Award. Girl Scouts recognized her with the Outstanding Volunteer Award. Linda was a longtime board member and past President of the League of Women Voters of Central Delaware County.

Linda was a strong supporter of Jefferson, including the Hospital Women's Board. She was active in the Faculty Wives Club and instrumental in organizing its annual art exhibit.

Linda was loved by family, friends, and community for her generous and caring spirit. In addition to her husband, she is survived by a daughter, two sons, a sister, and a brother.

CLASS NOTES

Alumni in Scranton and Wilkes Barre, Pennsylvania gathered to welcome Jefferson leaders on September 29, at a dinner hosted by Nicholas J. Ruggiero '66 (left) and Stephen E. Pascucci '48.

'28

Paul G. Holsinger of Martinsburg, PA celebrated his 100th birthday on July 24. His grandson, Steve Holsinger, wrote a tribute that appeared in the *Morrisons Cove Herald.* Dr. Holsinger has devoted many years to creating a comprehensive index of the Liebegott Collection for the Martinsburg Community Library. This index contains over 20,000 different names which he organized by hand.

'30

Leon L. Berns of Wynnewood, PA was featured in a large article in the *Jewish Exponent,* July 29, 1999. Dr. Berns is still practicing medicine in Philadelphia with his wife, Mildred, a registered nurse. Dr. Berns was also on the faculty at Jefferson for 63 years teaching the art and science of anatomy to first year medical students.

'48

Charles W. Anderson of Norfolk, VA is now retired and no longer a medical examiner, but is still working in the city's clinic for sexually transmitted diseases two days a week.

'56

Warren M. Levin is Chairman of the Medical Advisory Board of the Survive Until a Cure Foundation, a national organization that promotes various alternative therapies for patients with terminal illnesses. Dr. Levin now has an office in suburban Connecticut in addition to New York.

'59

Albert C. Price of Lancaster, PA has retired from the practice of pediatrics but continues to be active as senior advisor to the Safe Kids Program in Lancaster County, which he founded. Dr. Price, a pediatric cardiac specialist, was the PA Safe Kids Outstanding Coalition Volunteer in 1997. He was driven by the large number of children injured or killed in farm accidents. He and community leaders have worked together to promote farm safety locally and statewide. He has been recognized for his work among the Amish and Mennonite farm children.

'60 40th Reunion June 10

Herbert D. Kleber continues to work at developing new treatments for heroin and cocaine addiction, a field in which he is one of the country's foremost experts. The unit he set up at Columbia University College of Physicians and Surgeons was ranked number one in the country this year by *U.S. News and World Report.* Dr. Kleber tells the *Alumni Bulletin* that he has "some promising new treatment leads but no breakthrough imminent." His unit has six major studies underway that are funded by the National Institute on Drug Abuse. Kleber is a Professor of Psychiatry at Columbia, and Medical Director of the Center on Addiction and Substance Abuse (CASA). His publications include *The American Psychiatric Press Textbook of Substance Abuse Treatment* (1994), which is widely used by professionals.

'62

William V. Harrer has been President this year of the Medical Club of Philadelphia. "Many of our members are in fact from New Jersey," explains Dr. Harrer, who lives in Haddonfield and practices at Our Lady of Lourdes. In January he is succeeded as President by Robert Reinecke, M.D., a Professor of Ophthalmology at Jefferson.

'69

Jay S. Skyler of Key Biscayne, FL has been elected to the Board of Directors of Amylin Pharmaceuticals, headquartered in San Diego. Dr. Skyler is Professor of Medicine, Pediatrics, and Psychology and Co-director of the Behavioral Medicine Research Center at the University of Miami in Florida. He is also Director of the Operations Coordinating Center for the National Institute of Diabetes and Digestive and Kidney Disease's Diabetes Prevention Trial in Type One Diabetes. Dr. Skyler has served as President of the American Diabetes Association, and is currently Vice President of the International Diabetes Federation.

Amylin Pharmaceuticals is a pharmaceutical company focusing on metabolic disorders. They specialize in preclinical characterization of lead molecules and demonstration of the proof of their applicability to human health. The company has pioneered research of the hormone amylin and is developing SYMLIN (pramlintide acetate), a synthetic analog of human amylin, for the treatment of diabetes in people using insulin.

'70 30th Reunion June 10

Michael Ellis has contributed very generously to Jefferson Medical College to create a new scholarship, a program which is vitally important to the college. The Ellis family tradition of giving to Jefferson has been continued by Michael's son ***Jeffrey Ellis '98*** of Philadelphia.

Martin A. Tobey of Fort Worth, TX is still practicing cardiology. He and his wife, Judy, recently traveled to Budapest, Prague, and Vienna on an opera holiday.

'71

Paul M. Fernhoff of Atlanta, GA is completing a sabbatical year at the Centers for Disease Control working on policies for newborn screening.

'74

David A. Brent of Pittsburgh, PA continues as a Professor of Psychiatry at the University of Pittsburgh, directing a clinical research center that treats depressed and suicidal adolescents. "My greatest joy professionally," he says, "is helping young people to succeed at research."

Jay S. Greenspan, M.D., Director of Jefferson's Division of Neonatology, was the featured speaker at the recent Legacy Society reception. He is pictured with L. Roy Newman '49 and Mrs. Newman. The Legacy Society recognizes alumni and friends who have generously supported Jefferson through bequests, life income gifts, or other estate plans. The reception gave them the opportunity to talk with President Paul C. Brucker, M.D. and other Jefferson leaders.

Genetics of Nicotine Addiction May Explain Why It's Hard to Quit

For many people, even if they know the health problems that smoking causes, quitting is next to impossible. And getting hooked in the first place happened awfully fast. Of approximately 50 million smokers in the U.S., three fourths say they are addicted and two thirds say they want to quit. After surgery for lung cancer, nearly half of those who survive resume smoking. Among those whose larynxes have been removed, no fewer than 40 percent start smoking again.

Leone

Assistant Professor of Medicine Frank Leone PUD'97 is trying to figure out why some people can "go cold turkey" on cigarettes and nicotine, while others remain slaves to their addiction.

The reasons are many and complex. An intriguing theory is that nicotine addiction is due to a combination of both environmental influences and factors hardwired into the brain. Some people may be genetically more susceptible than others to become addicted to the nicotine in cigarettes.

Dr. Leone is now using a clinical trial to tease out the subtleties of nicotine addiction, particularly the genetic factors. He and his colleagues are looking at 800 pairs of siblings who smoke at least one pack of cigarettes a day and are nicotine-dependent. Four hundred pairs will be seen at Jefferson; the others will be studied at several other sites. Ashwin Patkar, M.D. of Jefferson's Department of Psychiatry is principal investigator.

The researchers are sampling genetic material from each sibling. "If you share a trait such as eye color, you're likely to share genes that control them," Leone says. "We're taking siblings who share a trait and looking for genes in those pairs that are present more frequently than would be expected.

"What predisposes you to certain behaviors is genetics. Some people can smoke for years, and one day decide to quit and never go back. Others try and try and are never able to stop. It may be too simplistic to say that some people have willpower and some don't. We like to think of each person as free-willed, but the fact is much of our behavior is wired.

"Despite similarities in nicotine levels in the blood, and in how people metabolize nicotine, they differ in their addictions," Leone says. He suspects that the behavioral trait for nicotine dependence may involve the genes that control how we perceive and process information.

"There have been meaningful twin studies showing that identical twins reared apart are more likely to both smoke than fraternal twins reared apart.

Dr. Leone and his coworkers hope to also conduct a study of unrelated people who share the behavioral trait to see if they share the same genes more frequently than those without the trait.

"We might find that there are several genes that interact with each other. Genetics is additive.

"Once we know the genes, we could figure out the biochemical pathway of the addiction," Leone says. "Ultimately, we'd like to find a drug that can inhibit the neural pathway involved in the need to keep lighting up."

Philadelphia Medical Society Honors Brady, Hughes, and Plotkin

The Philadelphia County Medical Society honored three Jeffersonians at its Awards Night in November 1999.

Brady

Luther W. Brady Jr. R'55 was recognized with the Strittmatter Award, the most prestigious prize of the evening. It is given for overall contribution to medicine or surgery.

Dr. Brady is known widely as a leader in radiation oncology and as a scholar and patron of the fine arts. He is currently the Hylda Cohn/American Cancer Society Professor at the Medical College of Pennsylvania and Hahnemann University. Brady is the founder and Editor of the *American Journal of Clinical Oncology* and a member of the editorial boards of 11 journals.

Dr. Brady has been president of nearly every major professional society relating to his specialty, and continues to be honored internationally for his work. He has participated in many committees of the Philadelphia County Medical Society, including service as Chair of the Center City Branch, Chair of the Cancer Committee, and Delegate to the Pennsylvania Medical Society.

Dr. Brady's interests also include the arts. He serves on numerous boards including those of the Philadelphia Museum of Art, the Santa Fe Opera Foundation, and the Opera Company of New Mexico.

Hughes

Alumna Wins the Appel Award

Tiffany A. Hughes '96, who remained at Jefferson after medical school for a one year residency in internal medicine, and is now a third year resident at Eastern Pennsylvania Psychiatric Institute, was presented with the PCMS's Appel Award. This is a monetary prize presented to a Philadelphia area psychiatric resident who submits the best paper on clinical psychiatry relating to an experience in therapy or in research.

Plotkin

Resident Wins the C. Nelson Davis Award

Randi L. Plotkin, M.D., a third year psychiatry resident at Jefferson, is the recipient of this year's C. Nelson Davis Award. This monetary prize is presented for the best paper relating to alcoholism or other addictive disorders affecting physicians. Dr. Plotkin's winning paper was entitled "Counter Transference in Two Settings: A Case Report." It focused on heroine abuse and addiction.

She Can Be as Tough as Her Cases, Though Not as High-profile

Question: What do these people have in common?

- John W. Hinckley Jr., attempted assassin of President Reagan
- Jim Bakker, disgraced televangelist
- Theodore Kaczynski, the Unabomber

Answer: They all underwent psychiatric evaluation by Sally A. Johnson '76, one of the nation's most respected forensic psychiatrists. Johnson is Chief of Psychiatric Services and Associate Warden for Health Services at the Federal Medical Center in Butner, North Carolina. She teaches at Duke University in both the Law School and the School of Medicine, in addition to being on the medical staff.

Defense lawyers said Kaczynski suffered from paranoid schizophrenia and had a phobia of being labeled mentally ill. Prosecutors countered that he was competent to stand trial. Kaczynski, who attempted suicide more than once and consistently refused to be examined by government psychiatrists, eventually capitulated and underwent an evaluation by Sally Johnson. He hoped to be found competent to act as his own trial attorney.

Johnson determined Kaczynski was competent. Her report to the judge linked Kaczynski's mental illness and the Unabomb campaign. Consistent with other individuals with persecutory types of delusions, she wrote, he was resentful and angry, and fantasizes and actually does resort to violence against those individuals and organizations that he believes are hurting him.

Sally Johnson's colleagues think her skills are superb. John Monahan, psychologist and law professor at the University of Virginia, says, "There's no question that the judge in the Kaczynski case chose [a forensic psychiatrist] well. Dr. Johnson is among the leading forensic psychiatrists in the country. She's known for her thorough evaluations and her balanced judgments. If anybody is up to this particularly challenging evaluation, Dr. Johnson is."

And Walter Dellinger, a former U.S. Solicitor General and a professor at Duke Law School, says he has known few lawyers or physicians who were able to combine the necessary professional detachment with the general sense of humanity that he sees in Johnson.

"So many people who go into this field are show people," says Dr. Keith Brodie, former Chair of the Psychiatry Department at Duke and former President of Duke University. They're flamboyant." But he calls Johnson "very low-key, unflappable, not pushy." Yet her evaluations make page one of the *New York Times*.

Not surprisingly, Dr. Johnson received the United States Attorney General's Award for Distinguished Service in July 1998 in Washington.

But while she obviously spends hours asking endless questions of her patients, she avoids answering questions from the public. "She's very intent about maintaining her professional integrity," her husband, William Johnson, a lawyer and a vice president of Carolina Power and Light, told the Raleigh, North Carolina *News and Observer*. She says "no" to Ted Koppel, the famed TV anchorman. "She never has given interviews and probably never will. And if I do, she will divorce me."

Johnson is a captain in the U.S. Public Health Service assigned to the Federal Bureau of Prisons. At Butner, she manages all medical services for 1000 inmates and serves as chief administrator for the 200-bed inpatient psychiatric hospital on site. Butner is one of three main psychiatry referral centers for males in the federal prison system.

While she was a student at Jefferson Medical College, Johnson accepted a public health scholarship, which required two years of payback. She took her residency at Duke University, where she had brief experience with prison populations. She scheduled her Public Health Service work after residency and chose the Bureau of Prisons for payback.

"Clearly prisons are an area of need in psychiatry," says Johnson, who refuses Ted Koppel, but kindly consents to an interview with the *Alumni Bulletin*. (This need at prisons is surely made clear by the nationally publicized lawsuit over care at the new maximum-security facility in southern Illinois.)

"Prisons have a population of individuals who are underserved," Johnson explains. "In a prison, you feel you can make a difference. What I like about the field has changed over time. My interest in psychiatry has always been in the treatment of psychosis. In prisons, certainly, you have ample opportunity to see psychosis. But more importantly, you get to follow patients over an extended time, which is something you rarely get to do in the general community. In prisons, you come to understand the course of illness, which is fascinating from a clinical standpoint."

The difficulty, she says, is that there are many treatment-resistant patients. One challenge is trying to deliver health care services in a system (prisons) where health care is not the primary mission. "It's necessary (assuring that the health care needs of prisoners are met), but it's not the major focus." Over the last few years, though, only part of Johnson's work has been clinical. She consults with prison systems around the country on establishing training programs and patient care programs.

The next time a high-profile, baffling criminal is in the paper, look for Sally Johnson's name as forensic psychiatrist.

Editor's Note: We Are Providing You the *Health Policy Newsletter*

To keep *Bulletin* readers informed about Jefferson, while containing mail costs, another publication is being shipped with the *Bulletin*. We believe you'll find that the *Health Policy Newsletter* tells you about topics that supplement those in the *Bulletin*. The *Health Policy Newsletter* is shipped quarterly, and describes health policy questions that Jefferson is studying.

Please let us know your thoughts by directing them to

Attention: Editor, *Alumni Bulletin*
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Email: Malcolm.Clendenin@mail.tju.edu

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Please tell the Alumni Office your e-mail address. It will be kept confidential, and will only be used to inform you about Jefferson activities. Simply send a message to jmc-alumni.office@mail.tju.edu

'77

Margaret M. Dunn has been appointed Associate Dean for Faculty and Clinical Affairs at Wright State University School of Medicine, effective September 1999.

Dr. Dunn is a Professor of Surgery at Wright State. She also has served as Associate Program Director of its integrated surgical residency and Co-director of Surgical Education at Miami Valley Hospital. Dr. Dunn recently was elected President of the American College of Surgeons, Ohio Chapter, and is a past President of the Association of Women Surgeons and the Dayton Surgical Society. She is a recipient of the Wright State University Academy of Medicine's Award for Excellence.

'80 20th Reunion June 10

Haynes "Tim" Cates Jr. of Wilmington, DE has been appointed Chief of the Division of Urology at Christiana Care Health Care System (the former Medical Center of Delaware). This division of the Department of Surgery at Christiana has been on *U.S. News and World Report's* "Best of" list for the past three years. Tim and his wife, Sally, are the proud parents of Burke, 12, and Kjell, 10.

Charles J. Dunton of Jefferson's Kimmel Cancer Center answers women's questions online about gynecologic cancers in "Ask Our Expert" on the Jefferson Health System website (www.jefferson-health.org). Dr. Dunton is an Associate Professor of Obstetrics and Gynecology at Jefferson. The web page enables browsers to ask Dunton questions online, and receive an online response within a week. Jefferson's gynecology program was named this year by *U.S. News and World Report* as among the best in the country.

'84

Maureen D. Francis has joined the faculty of Southern Illinois University School of Medicine as an Assistant Professor of Internal Medicine. She comes from Boonville Family Practice in Boonville, NC, where she was the Medical Director. Previously she was an Assistant Professor of Internal Medicine at the Uniformed Services University of Health Sciences in Bethesda, MD.

'86

Melissa Moore Brown of Flourtown, PA, was one of the featured speakers for the annual commencement and baccalaureate programs at Keuka College, Keuka Park, NY, where she is a member of the Class of '72. She presently serves as a member of the Keuka College Board of Trustees and is President and CEO of the Philadelphia Medical Press. In addition to her ophthalmology practice, she is cofounder of the Pennsylvania Physician Healthcare Plan.

'89

John J. Walsh IV and ***Eugenia Sarafidis Walsh*** are proud to announce the birth of Benjamin Christos, on June 23. Rita, age seven, Joseph, five, and Gabriela, three, are thrilled with their brother. John is now a hand surgeon and Assistant Professor of Orthopaedic Surgery at the University of South Carolina School of Medicine. Jenny returns to her previous position as Assistant Professor of Family and Preventive Medicine in January 2000 after an extended maternity leave. They live in Columbia, SC.

'90 10th Reunion June 10

John A. Osborne of Collegeville, TX has joined the staff at Baylor Medical Center at Grapevine. Dr. Osborne's specialty is cardiovascular physiology.

Mohan Suntharalingam of Baltimore, MD was featured in the June issue of the *AAMC Reporter,* a national publication of the Association of American Medical Colleges. The article described "A Day in the Life of a Junior Faculty Member." Dr. Suntha is an Assistant Professor of Radiation Oncology at the University of Maryland.

Scott Memorial Library privileges for medical college alumni including postgraduate alumni: You may obtain a library card from the Scott Memorial Library. On your first visit to the library, please present your blue plastic alumni identification card and one form of photo identification (such as a driver's license) at the circulation desk window located on the second floor of the library. A barcode will be attached to your alumni ID card for no fee, and you will be able to use it to borrow books and to avail yourself of many of the services of the library free of charge.

Each time you visit the library, you will be required to show your alumni ID card to the security officer stationed in the lobby. You may also be required to produce photo identification. This is for the protection of the staff and patrons of the library.

If you have misplaced your alumni ID card, you may call the JMC Alumni Office (215 955 7750). After we have verified your status in the alumni database, we will mail you an alumni ID card and a sheet listing the library services available to alumni library card holders.

'92

Diane L. Ching of Ambler, PA is now a pediatrician at Meadowbrook Pediatrics and Holy Redeemer Hospital. She and ***Lynn Silver Nugent*** have gotten together a few times since both their children happened to attend the same preschool class last year.

'93

Dawn A. Demangone of Philadelphia, PA married Dr. Russell Yoon in October. Dawn is now the Assistant Residency Director in Emergency Medicine, and Co-director of Medical Student Education in Emergency Medicine at Temple University.

Scott A. Rushton has joined the Department of Orthopaedic Surgery at the University of Pennsylvania Health System. Dr. Rushton specializes in complex spine surgery and has published several papers on the topic. He completed his residency in orthopaedic surgery at Jeff and performed a fellowship in spine surgery at University Hospitals of Cleveland/Case Western Reserve University.

'94

Shmuel Shoham is currently living in Brighton, MA and happily married to Ruth Polk, a fellow in infectious diseases at Boston Medical Center. He is involved in researching the immune response to fungi.

'96

Matthew R. Panahandeh was married in October 1998 to Michelle Rathgeb, one of his fellow residents in the Department of Medicine at the University of Pittsburgh. Jeffersonians in attendance included ***Joseph J. Murphy III***, his best man, ***Stephen D. Moy, Jason G. Wilmoth, Mark A. Taylor, Jeff Namey, Brett Opell***, and ***Stephanie L. Archer***.

Julie Toms Poludniak of Elkton, MD and husband, Tim, are proud to announce the birth of their first child, Sarah, born August 18.

'97

Charles P. McClure of Springfield, PA is serving as Chief Resident in Family Medicine at Bryn Mawr Hospital for 1999-2000.

'99

Anand V. Germanwala was one of the senior medical students honored at Jefferson in 1998–99 with Beach Scholarships. He is now training in orthopaedics at Penn State Geisinger Health System in Hershey, PA.

Postgraduate Alumni

Yoogoo Kang AN'78 has been appointed the Samuel Israel Professor and Chair of Anesthesiology at Tulane University School of Medicine in New Orleans. Dr. Kang is one of several Jeffersonians recently appointed to important posts in anesthesiology, including ***Stephen E. Abram '70,*** who is now Chair of Anesthesiology at the University of New Mexico in Albuquerque.

Dennis L. Priolo DR'88 has joined the Landmark Medical Center in Woonsocket, RI. Dr. Priolo is certified by the American Board of Radiology.

Maromi Nei N'99 has been appointed a staff member of the Comprehensive Epilepsy Center at Jefferson, and Assistant Professor of Neurology. Dr. Nei recently completed a fellowship a the center, which is one of the largest epilepsy programs in the world and is directed by Michael Sperling, M.D. Dr. Nei is board certified in psychiatry and neurology. She completed a neurology residency at the Hospital of the University of Pennsylvania, where she received the Samuel Zeritsky Clinical Research Prize. Her research has been published in journals including *Epilepsia* and *Neurology*.

The staff of neurologists, neurosurgeons, psychologists, and neuroscientists at Jefferson's center provide a wide array of services including video EEG monitoring, an internationally renowned epilepsy surgery program, genetic counseling, specialty care during pregnancy, neuropsychological evaluations, psychological care, cognitive rehabilitation, social support, and community education.

Graduate Studies

Clara M. Ambrus, Ph.D.'55 has been elected to the Board of Directors of Aethlon Medical, headquartered in San Diego. The inventor of the Hemopurifier line of blood purification products, Dr. Ambrus is the founder of Hemex, Incorporated, a subsidiary of Aethlon. A Research Professor of Pharmacology, Pediatrics, and Obstetrics-gynecology at SUNY-Buffalo, she has expertise in hematology, thrombosis-hemorrhage, respiratory distress syndromes, and immobilized enzymes. She has over 200 scientific publications to her credit.

Readers are encouraged to submit nominations for the Medical College Alumni Achievement Award: The Achievement Award Committee of the alumni association is charged with the final selection. Please direct curricula vitae and bibliographies of medical college graduates, including postgraduate alumni, whose professional activities are sufficiently outstanding to warrant consideration to "Attention: Achievement Award Committee," 1020 Locust Street M-41, Philadelphia, PA 19107.

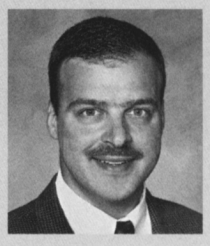
YOUNG INVESTIGATOR

Nation's First Clinical Trial of Methods to Treat Paralyzing Spinal Cord Injury

A first-ever randomized study to determine the best therapy for treating a paralyzing spinal cord injury, began this fall at the Regional Spinal Cord Injury Center at Magee Rehabilitation Hospital and Jefferson. Funded by the National Institute of Child Health and Human Development, the study will continue for five years.

"Until now, there have been no scientific studies to define which mode of therapy works best for spinal cord injury," explains principal investigator John Ditunno Jr., M.D., Director of the Regional SCI Center.

Patients who have sustained an acute but incomplete spinal cord injury will be eligible for the study. Approximately half of those who are treated at the Regional SCI Center fall into this category. Participants will be treated with either conventional therapy which utilizes daily mobility retraining, or a combination of conventional interventions and body weight-supported ambulation therapy.



Saulino

"We want to determine which type of therapy produces better ambulation status or walking ability," says Michael Saulino PM'97, Instructor in Rehabilitation Medicine and Assistant Director of Resident Education, "and whether motor skills are improved."

The theoretical basis of body weight-supported therapy is the concept of a central pattern generator. "This is based on a belief that the human spinal cord has an intelligence all its own that can generate steplike electrical patterns when exposed to sensations like walking," Ditunno explains.

Patients must have sustained their spinal cord injury within eight weeks of taking part in the study, and have some feeling or movement below the position of the injury. Subjects undergoing the weight-supported ambulation, which is done at Magee, are placed in a parachute harness and positioned over a treadmill. Once the treadmill belt is moving, the investigation team, which includes physical therapists, assist in moving the patient's legs in a way that should optimize sensory inputs. Clinical research has shown that patients with certain types of SCI who undergo this type of therapy gain enhanced locomotor activity.

Dr. Saulino anticipates that approximately 25 patients will be enrolled annually. The Regional SCI Center is one of five centers nationwide participating in the study.

Jefferson, in affiliation with Magee, is designated as one of the nation's 18 Regional Research Spinal Cord Injury Centers, and the only one in the Delaware Valley. It is also federally designated as a Model System SCI Center.

Jefferson and Magee, along with MossRehab—all members of the Jefferson Health System—were named this year by *U.S. News and World Report* in its "America's Best Hospitals" issue as among the foremost rehabilitation programs in the nation—the only Philadelphia providers to achieve this honor.

The Regional SCI Center, which has treated more than 2,500 individuals, provides a multidisciplinary system of acute care and rehabilitation. It offers services from the moment of injury, through acute and rehabilitation phases, to followup care and reintegration into the community. With over 70 percent of persons with SCI admitted within three days of injury, the center has demonstrated a mortality rate of five percent (as compared to a 17 percent national average) and has significantly reduced the severe secondary complications.